Your Journey with RITUXAN® and RITUXAN HYCELA™

Please see pages 57-65 and accompanying Full Prescribing Information for RITUXAN and RITUXAN HYCELA, including their respective Medication Guides, for Important Safety Information.
Indications for RITUXAN
RITUXAN® (rituximab) is indicated for the treatment of:
- Low-grade or follicular CD20-positive non-Hodgkin’s lymphoma as a single-agent therapy in patients whose disease recurred or did not respond to initial treatment
- Follicular CD20-positive non-Hodgkin’s lymphoma as an initial treatment with chemotherapy, and in patients whose initial treatment was successful, as a single-agent follow-up therapy
- Low-grade CD20-positive non-Hodgkin’s lymphoma as a single-agent follow-up therapy for patients who did not progress on initial treatment with CVP chemotherapy
- CD20-positive diffuse large B-cell non-Hodgkin’s lymphoma as an initial treatment in combination with CHOP chemotherapy
- CD20-positive chronic lymphocytic leukemia in combination with FC chemotherapy as an initial treatment or as a treatment after disease has recurred

People with serious infections should not receive RITUXAN
It is not known if RITUXAN is safe or effective in children

Important Safety Information about RITUXAN
What is the most important information I should know about RITUXAN?
Tell your doctor right away about any side effect you experience. RITUXAN can cause serious side effects that can lead to death, including:

Infusion Reactions: may occur during or within 24 hours of your infusion. Your doctor should give you medicines before your treatment. Symptoms can include hives, rash, itching, facial or oral swelling, sudden cough, shortness of breath, difficulty breathing, weakness, dizziness, feeling faint, racing heart, chest pain

Severe Skin and Mouth Reactions: symptoms can include painful sores, ulcers, or blistering on your skin, lips or mouth; peeling skin; rash; or pustules

Hepatitis B Virus (HBV) Reactivation: may cause serious liver problems including liver failure and death. If you have had hepatitis B or are a carrier of HBV, receiving RITUXAN could cause the virus to become an active infection again. You should not receive RITUXAN if you have active HBV liver disease. Your doctor will do blood tests to check for HBV infection prior to treatment and will monitor you during and for several months following your treatment

Please see pages 57-65 and accompanying full Prescribing Information for RITUXAN and RITUXAN HYCELA, including their respective Medication Guides, for additional Important Safety Information.

Indications for RITUXAN HYCELA
RITUXAN HYCEL® (rituximab/hyaluronidase human) is a prescription medicine used to treat adults with:
- Follicular Lymphoma as a single-agent therapy in patients whose disease recurred or did not respond to initial treatment
- Follicular Lymphoma as an initial treatment with chemotherapy and, in patients whose initial treatment was successful, as a single-agent follow-up therapy
- Follicular Lymphoma as a single-agent follow-up therapy for patients who did not progress on initial treatment with CVP chemotherapy
- Diffuse Large B-Cell Lymphoma (DLBCL) as an initial treatment in combination with CHOP or other anthracycline-based chemotherapy regimens
- Chronic Lymphocytic Leukemia (CLL) in combination with FC chemotherapy as an initial treatment or as a treatment after disease has recurred

You can only receive RITUXAN HYCELA after you receive at least 1 full dose of intravenous (IV) RITUXAN® (rituximab).
Read the IV RITUXAN Medication Guide for more information about severe infusion reactions, which usually happen during the first dose with IV RITUXAN.
RITUXAN HYCELA is not for use to treat medical conditions other than cancers
It is not known if RITUXAN HYCELA is safe and effective in children

Important Safety Information about RITUXAN HYCELA
What is the most important information I should know about RITUXAN HYCELA?
RITUXAN HYCELA can cause serious side effects that can lead to death, including:

Severe skin and mouth reactions:
Tell your healthcare provider or get medical help right away if you get any of these symptoms at any time during your treatment with RITUXAN HYCELA: painful sores or ulcers on your skin, lips or mouth; peeling skin; rash; or pustules

Hepatitis B virus (HBV) reactivation:
Before you receive RITUXAN HYCELA, your doctor will do blood tests to check for HBV infection. If you have had hepatitis B or are a carrier of hepatitis B virus, receiving RITUXAN HYCELA could cause the virus to become an active infection again. Hepatitis B reactivation may cause serious liver problems including liver failure and death. Your healthcare provider will monitor you for hepatitis B infection during and for several months after you stop receiving RITUXAN HYCELA.
Tell your healthcare provider right away if you get worsening tiredness, or yellowing of your skin or white part of your eyes during treatment with RITUXAN HYCELA

Please see pages 57-65 and accompanying full Prescribing Information for RITUXAN and RITUXAN HYCELA, including their respective Medication Guides, for additional Important Safety Information.
Important Safety Information about RITUXAN (cont’d)

RITUXAN can cause serious side effects that can lead to death, including:

Progressive Multifocal Leukoencephalopathy (PML): a rare, serious brain infection that can lead to severe disability and death and for which there is no known prevention, treatment, or cure. Symptoms can include difficulty thinking, loss of balance, changes in speech or walking, weakness on one side of your body, or blurred or lost vision.

Important Safety Information about RITUXAN HYCELA (cont’d)

RITUXAN HYCELA can cause serious side effects that can lead to death, including:

Progressive multifocal leukoencephalopathy (PML): PML is a rare, serious brain infection caused by a virus that can happen in people who receive RITUXAN HYCELA. People with weakened immune systems can get PML. PML can result in death or severe disability. There is no known treatment, prevention, or cure for PML. Tell your healthcare provider right away if you have any new or worsening symptoms or if anyone close to you notices these symptoms: confusion; dizziness or loss of balance; difficulty walking or talking; decreased strength or weakness on one side of your body; vision problems, such as blurred or lost vision.

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Please contact your healthcare treatment team with any questions that you may have. The information provided in this brochure is meant for informational purposes only. It is not meant to replace your physician’s medical advice.

Important Safety Information about RITUXAN HYCELA (cont’d)

RITUXAN HYCELA can cause serious side effects that can lead to death, including:

- Progressive multifocal leukoencephalopathy (PML): A rare, serious brain infection caused by a virus that can happen in people who receive RITUXAN HYCELA. People with weakened immune systems can get PML. PML can result in death or severe disability. There is no known treatment, prevention, or cure for PML. Tell your healthcare provider right away if you have any new or worsening symptoms or if anyone close to you notices these symptoms: confusion; dizziness or loss of balance; difficulty walking or talking; decreased strength or weakness on one side of your body; vision problems, such as blurred or lost vision.
What is FL?

Follicular lymphoma, or FL, is a cancer of the immune system. FL occurs in lymphocytes, a type of white blood cell. These cells are an important part of your immune system and help defend your body from infection. When you have FL, too many white blood cells that are affected by the disease build up in your lymph nodes, blood, and bone marrow. They may also build up in your spleen (an organ in your immune system) and cause swelling of this organ.
Signs and symptoms of FL

Everyone experiences follicular lymphoma (FL) differently. Symptoms may not show up until lymphoma is advanced. It is important to pay attention to how your FL may be affecting you. Tell your doctor if you notice any symptoms or changes in your health.

Patients with FL often will notice an area of painless swelling on the body, such as on the neck, underarm, or groin. As a slow-growing type of lymphoma, FL does not always require immediate treatment.

FL cannot be diagnosed by symptoms alone. In fact, you are often not the first to notice your FL. It is usually detected by routine checkups, or blood work for other health issues. Your doctor will need to use medical tests to diagnose your FL. Medical tests will also tell where FL is in your body.

Possible symptoms you should watch for include:
- Enlarged lymph nodes
- Fever, fatigue, and night sweats
- Unexplained weight loss
- Severe or frequent infections
- Easy bruising or bleeding
- Numbness or tingling in feet and/or hands
- Headaches and/or blurry vision
- Swelling in your lymph nodes, liver, or spleen
- An increase in the number of abnormal white blood cells
- A decrease in the number of normal blood cells

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- Headaches and/or blurry vision
- Swelling in your lymph nodes, liver, or spleen
- An increase in the number of abnormal white blood cells
- A decrease in the number of normal blood cells

Understanding medical tests for FL

Common tests include:
- Routine tests such as physical exam, blood cell counts, and bone marrow biopsy
- Flow cytometry—a sample of your cells is examined using a laser beam and a computer to find out the type of cancer and the number of cells involved
- Imaging tests such as PET-CT or CT scans—these scans produce pictures of the inside of your body that help show where FL is

Possible symptoms you should watch for include:
- Enlarged lymph nodes
- Fever, fatigue, and night sweats
- Unexplained weight loss
- Severe or frequent infections
- Easy bruising or bleeding
- Numbness or tingling in feet and/or hands
- Headaches and/or blurry vision
- Swelling in your lymph nodes, liver, or spleen
- An increase in the number of abnormal white blood cells
- A decrease in the number of normal blood cells

Your doctor may be looking for:
- Enlarged lymph nodes
- Fever, fatigue, and night sweats
- Unexplained weight loss
- Severe or frequent infections
- Easy bruising or bleeding
- Numbness or tingling in feet and/or hands
- Headaches and/or blurry vision
- Swelling in your lymph nodes, liver, or spleen
- An increase in the number of abnormal white blood cells
- A decrease in the number of normal blood cells

While you are being treated and after your treatment concludes, your doctor will continue to monitor your FL. 

Symptoms of FL may be seen in other conditions as well. Only your doctor will be able to tell if your symptoms are related to FL.
The 4 stages of FL

Staging describes how far lymphoma has spread. Keep in mind that even the most advanced stages of follicular lymphoma (FL) (Stage III and Stage IV) are common and can be treated.

One group of lymph nodes is affected either above or below the diaphragm.

Two or more groups of lymph nodes are affected either above or below the diaphragm.

Lymph nodes are affected both above and below the diaphragm, or above the diaphragm with spleen involvement.

Lymphoma is found in bone marrow and/or organs outside of the lymph nodes and spleen.

FL is not curable, but can be managed over time. Or you may need treatment again because the disease has advanced (relapse). As a result, the goals of treatment are to relieve symptoms, stop the cancer from getting worse, or achieve remission.

FL can be treated in a number of ways, including antibody therapy and/or chemotherapy. Often, doctors will combine the 2 types of treatment.

Goals of treatment for FL

Treatment goals and options depend on how much your symptoms are affecting you:

- When you don’t have symptoms, close monitoring is usually preferred over treatment. This is often referred to as “watch and wait.”
- When symptoms appear or worsen, treatment aims to stop the FL from progressing.

Once you begin treatment, your doctor will need to regularly check:

- Your symptoms
- The size of your lymph nodes, liver, or spleen
- Your blood count measures

Treatments may vary from patient to patient. And when you’ve been treated before, remember that your response may not be as good the second time around. Still, it is important to understand what options are available and to discuss your treatment goals with your doctor.

**DIAGNOSIS:** FL

**DEFINITION:**

- **FL:** The disease is not curable, but can be managed over time. Or you may need treatment again because the disease has advanced (relapse). As a result, the goals of treatment are to relieve symptoms, stop the cancer from getting worse, or achieve remission.

- **Relapse:** The return of a disease, or the signs and symptoms of a disease after a period of improvement.
- **Remission:** A term used to describe a patient’s response to treatment. Partial remission means the cancer is improved, but evidence of the cancer remains. Complete remission means all signs and symptoms of cancer have disappeared for a period of time, although cancer may still be in the body.

- **Diaphragm:** The muscle that divides the chest cavity from the abdominal cavity.
What is DLBCL?

**LYMPH NODES**
Store white blood cells and help remove harmful substances from the body.

**SPLINE**
Helps the body fight infection. Filters damaged blood cells, bacteria, and cell waste out of the blood.

**BONE MARROW**
Makes red blood cells, white blood cells, and platelets.

Diffuse large B-cell lymphoma, or DLBCL, is a cancer of the immune system. DLBCL occurs in lymphocytes, a type of white blood cell. These cells are an important part of your immune system and help defend your body from infection. When you have DLBCL, too many white blood cells that are affected by the disease build up in your lymph nodes, blood, and bone marrow. They may also build up in your spleen (an organ in your immune system) and cause swelling of this organ.
Everyone experiences diffuse large B-cell lymphoma, or DLBCL, differently. Because DLBCL is a fast-growing lymphoma, symptoms may show up sooner than in some others. It is important to pay attention to how your DLBCL may be affecting you. Tell your doctor if you notice any symptoms or changes in your health. DLBCL can arise in lymph nodes or outside of the lymphatic system in the gastrointestinal tract, testes, thyroid, skin, breast, bone, or brain. Fast-growing lymphomas such as DLBCL usually require immediate treatment.

- Enlarged lymph nodes
- Fever, fatigue, and night sweats
- Unexplained weight loss
- Severe or frequent infections
- Easy bruising or bleeding
- Headaches and/or blurry vision
- Numbness or tingling in feet and/or hands
- An increase in the number of abnormal white blood cells
- A decrease in the number of normal blood cells
- Swelling in your lymph nodes, liver, or spleen
- Flow cytometry—a sample of your cells is examined using a laser beam and a computer to find out the type of cancer and the number of cells involved
- Imaging tests such as PET-CT or CT scans—these scans produce pictures of the inside of your body that help show where DLBCL is

Possible symptoms you should watch for include:

Your doctor may be looking for:

Symptoms of DLBCL may be seen in other conditions as well. Only your doctor will be able to tell if your symptoms are related to DLBCL.

Understanding medical tests for DLBCL

DLBCL cannot be diagnosed by symptoms alone. In fact, you are often not the first to notice your DLBCL. It is usually detected by routine checkups, or blood work for other health issues. Your doctor will need to use medical tests to diagnose your DLBCL. Medical tests will also tell where DLBCL is in your body.

Common tests include:

- Routine tests such as physical exam, blood cell counts, and bone marrow biopsy
- Flow cytometry—a sample of your cells is examined using a laser beam and a computer to find out the type of cancer and the number of cells involved
- Imaging tests such as PET-CT or CT scans—these scans produce pictures of the inside of your body that help show where DLBCL is
The 4 stages of DLBCL

Staging describes how far lymphoma has spread. Keep in mind that even the most advanced stages of diffuse large B-cell lymphoma (DLBCL) (Stage III and Stage IV) are common and can be treated.

## STAGE I
One group of lymph nodes is affected either above or below the diaphragm.

## STAGE II
Two or more groups of lymph nodes are affected either above or below the diaphragm.

## STAGE III
Lymph nodes are affected both above and below the diaphragm, or above the diaphragm with spleen involvement.

## STAGE IV
Lymphoma is found in bone marrow and/or organs outside of the lymph nodes and spleen.

### Goals of treatment for DLBCL

Overall, some of the goals of treatment for DLBCL are to:

- Relieve symptoms
- Stop the cancer from getting worse
- Get the disease into **remission**

If your doctor says you need treatment, there are many options to help manage your DLBCL. These include antibody therapy and/or chemotherapy. Often, doctors will combine these 2 types of treatment.

The appropriate treatment for you depends on a number of factors. These include:

- The stage of DLBCL: how much DLBCL there is and where it is in your body
- Your personal characteristics, such as age and overall health

Once you begin treatment, your doctor will need to regularly check:

- Your symptoms
- The size of your lymph nodes, liver, or spleen
- Your blood count measures

**Remission**: A term used to describe a patient’s response to treatment. Partial remission means the cancer is improved, but evidence of the cancer remains. Complete remission means all signs and symptoms of cancer have disappeared for a period of time, although cancer may still be in the body.

**Diaphragm**: The muscle that divides the chest cavity from the abdominal cavity.

**Definition**:

- **Stage I**: Lymphoma is found in bone marrow and/or organs outside of the lymph nodes and spleen.
- **Stage II**: Lymph nodes are affected either above or below the diaphragm.
- **Stage III**: Lymph nodes are affected both above and below the diaphragm, or above the diaphragm with spleen involvement.
- **Stage IV**: Lymphoma is found in bone marrow and/or organs outside of the lymph nodes and spleen.
What is CLL?

**Spleen**
Helps the body fight infection. Filters damaged blood cells, bacteria, and cell waste out of the blood.

**Bone Marrow**
Makes red blood cells, white blood cells, and platelets.

**Lymph Nodes**
Store white blood cells and help remove harmful substances from the body.

Chronic lymphocytic leukemia, or CLL, is a cancer of the immune system. CLL is the most common chronic leukemia in the United States. In people with CLL, too many white blood cells (known as lymphocytes) build up in the blood, bone marrow, spleen, and lymph nodes. Over time, these cells may crowd healthy cells, resulting in fewer normal blood cells and platelets.
Signs and symptoms of CLL

Everyone experiences chronic lymphocytic leukemia, or CLL, differently. It is important to pay attention to how your CLL may be affecting you. Tell your doctor if you notice any symptoms or changes in your health.

Possible symptoms you should watch for include:
- Swollen lymph nodes in the neck, armpit, or groin. This swelling can be painless
- Discomfort or a feeling of fullness in the abdomen
- Feeling very tired or weak
- Feeling short of breath
- Fever, night sweats, or weight loss
- Infections of the skin or body

While you are being treated and after your treatment concludes, your doctor will continue to monitor your CLL.

Possible symptoms you should watch for include:
- Swelling in your lymph nodes, liver, or spleen
- An increase in the number of CLL cells
- A decrease in the number of normal blood cells

Your doctor may be looking for:
- Swelling in your lymph nodes, liver, or spleen
- An increase in the number of CLL cells
- A decrease in the number of normal blood cells

Symptoms of CLL may be seen in other conditions as well. Only your doctor will be able to tell if your symptoms are related to CLL.

Understanding medical tests for CLL

CLL does not always cause symptoms. In early stages of CLL, you are less likely to be bothered by symptoms. CLL is usually detected by routine check-up or bloodwork for other issues. Your doctor will need to use medical tests to diagnose CLL.

Common tests to diagnose CLL include:
- Physical exam—your doctor will give you a physical exam to check for swollen lymph nodes, liver, or spleen (an organ in your abdomen), and other signs of CLL
- Blood cell counts—your blood is taken through a vein and examined. Most people with CLL have a high white blood cell count
- Biopsy—a lymph node or small sample of bone marrow is removed and viewed under a microscope to see if you have CLL
- Flow cytometry—your blood is examined to find out the type of cancer and number of cells involved

Common tests to find out where CLL is in your body include:
- Imaging tests such as X-rays, CT scans, MRI scans, or PET scans—these are pictures of the inside of your body that help show where the CLL is
The stages of chronic lymphocytic leukemia (CLL) are used to describe how far along your disease is. Note that the risk is the likelihood that the CLL may advance and become more serious. Ask your doctor or nurse to tell you the stage and risk of your CLL. Then discuss what it may mean for you.

### The stages of CLL

<table>
<thead>
<tr>
<th>CLL stage/risk</th>
<th>How far along your disease is</th>
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<td>STAGE 0: Low risk</td>
<td>High lymphocyte count in the blood</td>
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<td>STAGE 1: Intermediate risk</td>
<td>High lymphocyte count in the blood</td>
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<td>STAGE 2: Intermediate risk</td>
<td>Swollen lymph nodes</td>
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<tr>
<td>STAGE 3: High risk</td>
<td>High lymphocyte count in the blood</td>
</tr>
<tr>
<td>STAGE 4: High risk</td>
<td>Low red blood cell count (anemia)</td>
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- Enlarged liver or spleen
- With or without swollen lymph nodes, liver, or spleen

### Goals of treatment for CLL

You may just be starting treatment for your CLL. Or you may need treatment again because the disease has advanced (relapse).

#### Some goals of treatment are to:
- Relieve symptoms
- Stop the cancer from getting worse
- Get the disease into partial or complete remission

There are many treatment options for CLL. The appropriate treatment for you depends on a number of factors. These include:
- The stage of CLL—how far along your disease is
- Your personal characteristics—such as age and overall health

Treatments may vary from patient to patient. And when you’ve been treated before, remember that your response may not be as good the second time around. Still, it is important to understand what options are available and to discuss your treatment goals with your doctor.
Important Safety Information about RITUXAN (cont’d)

What are additional possible serious side effects of RITUXAN?

Tell your doctor right away about any side effect you experience. RITUXAN can cause serious side effects that can lead to death, including:

- Tumor Lysis Syndrome (TLS): may cause kidney failure and the need for dialysis treatment, abnormal heart rhythm, and can lead to death. Your doctor may give you medicines before your treatment to help prevent TLS.

About RITUXAN®

RITUXAN is used to treat FL, DLBCL, and CLL

RITUXAN is not chemotherapy
- Follicular Lymphoma (FL): alone or with certain chemotherapy medicines
- Diffuse Large B-Cell Lymphoma (DLBCL): with certain other chemotherapy medicines in people who have not had previous treatment for their DLBCL
- Chronic Lymphocytic Leukemia (CLL): with the chemotherapy medicines fludarabine and cyclophosphamide

People with serious infections should not receive RITUXAN
It is not known if RITUXAN is safe or effective in children.

RITUXAN targets and attaches to the CD20 protein found on the surface of FL, DLBCL, and CLL cells and some healthy blood cells. Once attached to the CD20 protein, RITUXAN is thought to work in different ways including:

1. By helping your own immune system destroy the cancer cells
2. By destroying the cancer cells on its own

In addition, RITUXAN can also harm healthy cells in your body.

RITUXAN can be an important part of treatment for many patients with FL, DLBCL, and CLL.

Please see pages 57-59 and accompanying RITUXAN full Prescribing Information, including Medication Guide, for additional Important Safety Information.
What should I tell my doctor before receiving RITUXAN?

Before receiving RITUXAN, tell your doctor if you:

- have had a severe infusion reaction to RITUXAN in the past
- have a history of heart problems, irregular heart beat, or chest pain
- have lung or kidney problems
- have an infection or weakened immune system
- have or have had any severe infections including:
  - Hepatitis B virus (HBV)
  - Hepatitis C virus (HCV)
  - Cytomegalovirus (CMV)
  - Herpes simplex virus (HSV)
  - Varicella zoster virus (chickenpox or shingles)
  - Parvovirus B19
  - West Nile virus
- have had a recent vaccination or are scheduled to receive vaccinations. You should not receive certain vaccines before or after you receive RITUXAN. Tell your doctor if anyone in your household is scheduled to receive a vaccination. Some types of vaccines can spread to people with a weakened immune system and cause serious problems
- have taken RITUXAN for granulomatosis with polyangiitis (GPA) or microscopic polyangiitis (MPA) in the past
- have any other medical conditions

- are pregnant or planning to become pregnant. RITUXAN may affect the white blood cell counts of your unborn baby. It is not known if RITUXAN may harm your unborn baby in other ways
- Women who are able to become pregnant should use effective birth control (contraception) while using RITUXAN and for 12 months after you finish treatment. Talk to your doctor about effective birth control
- are breast-feeding or plan to breast-feed. It is not known if RITUXAN passes into your breast milk. You and your doctor should decide the best way to feed your baby if you receive RITUXAN

Tell your doctor about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. Especially tell your doctor if you take or have taken:

- a Tumor Necrosis Factor (TNF) inhibitor medicine
- a Disease Modifying Anti-Rheumatic Drug (DMARD)

If you are not sure if your medicine is one listed above, ask your doctor or pharmacist.

Know the medicines you take. Keep a list of them to show to your doctor and pharmacist when you get a new medicine. Do not take any new medicine without talking with your doctor.

Please see pages 57-59 and accompanying RITUXAN full Prescribing Information, including Medication Guide, for additional Important Safety Information.
About RITUXAN HYCELA™

Important Safety Information about RITUXAN HYCELA (cont’d)

What is the most important information I should know about RITUXAN HYCELA?

RITUXAN HYCELA can cause serious side effects that can lead to death, including:

- Serious allergic reactions and other severe reactions: Serious allergic reactions, and reactions due to release of certain substances by your body that can lead to death, can happen with rituximab products, including RITUXAN HYCELA.

- Skin reactions at or near the injection site (local), including injection site reactions can happen with RITUXAN HYCELA. Symptoms at or near the injection site may include: pain, swelling, hardness, redness, bleeding, itching, and rash. These reactions sometimes happen more than 24 hours after an injection of RITUXAN HYCELA.

Tell your healthcare provider or get medical help right away if you get any of these symptoms during or after an injection of RITUXAN HYCELA: hives (red itchy welts) or rash; itching; swelling of your lips, tongue, throat, or face; sudden cough; shortness of breath, difficulty breathing, or wheezing; weakness; dizziness or feeling faint; palpitations (feeling like your heart is racing or fluttering); chest pain; fever; chills or shaking chills.

What is RITUXAN HYCELA?

RITUXAN HYCELA is a prescription medicine used to treat adults with:

- Follicular Lymphoma (FL): alone or with certain chemotherapy medicines
- Diffuse Large B-Cell Lymphoma (DLBCL): with certain other chemotherapy medicines in people who have not had previous treatment for their DLBCL
- Chronic Lymphocytic Leukemia (CLL): with the chemotherapy medicines fludarabine and cyclophosphamide

You can only receive RITUXAN HYCELA after you receive at least 1 full dose of intravenous (IV) RITUXAN® (rituximab). Read the IV RITUXAN Medication Guide for more information about severe infusion reactions, which usually happen during the first dose with IV RITUXAN.

RITUXAN HYCELA is not for use to treat medical conditions other than cancers.

It is not known if RITUXAN HYCELA is safe and effective in children.

Your healthcare provider should monitor you for side effects for at least 15 minutes after you receive RITUXAN HYCELA.
Before you receive RITUXAN HYCELA, tell your healthcare provider about all of your medical conditions, including if you:

- have had a severe reaction to a rituximab product or RITUXAN HYCELA
- have a history of heart problems, irregular heart beat or chest pain
- have lung or kidney problems
- have an infection or weakened immune system
- have or have had any severe infections including:
  - Hepatitis B virus (HBV)
  - Hepatitis C virus (HCV)
  - Cytomegalovirus (CMV)
  - Herpes simplex virus (HSV)
  - Parvovirus B19
  - Varicella zoster virus (chickenpox or shingles)
  - West Nile virus

What should I tell my doctor before receiving RITUXAN HYCELA?

- have had a recent vaccination or are scheduled to receive vaccinations. You should not receive certain vaccines before or during treatment with RITUXAN HYCELA
- are pregnant or plan to become pregnant. Talk to your healthcare provider about the risks to your unborn baby if you receive RITUXAN HYCELA during pregnancy. Females who are able to become pregnant should use effective birth control (contraception) during treatment with RITUXAN HYCELA and for 12 months after the last dose of RITUXAN HYCELA. Talk to your healthcare provider about effective birth control.
- are breastfeeding or plan to breastfeed. It is not known if RITUXAN HYCELA passes into your breast milk. Do not breastfeed during treatment and for at least 6 months after your last dose of RITUXAN HYCELA. Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

Please see pages 60-65 and accompanying RITUXAN HYCELA full Prescribing Information, including Medication Guide, for additional Important Safety Information.
What to expect during treatment
Initial treatment for FL

Your first dose will be RITUXAN® (rituximab) with CHOP or CVP chemotherapy. If you were able to receive and tolerate at least one full dose of RITUXAN, you may receive RITUXAN HYCELA™ (rituximab/hyaluronidase human) with CHOP or CVP chemotherapy during future cycles of treatment. Chemotherapy and RITUXAN or RITUXAN HYCELA work together in different ways to fight cancer. The goal in using this combination of drugs is to keep your cancer from getting worse.

You will have up to 8 cycles, or rounds, of treatment. Each cycle will last 21 days. Treatment occurs on the first day of each cycle and is followed by 20 days of rest and recovery. Most people will complete their treatment in about 6 months.

Important Safety Information about RITUXAN (cont’d)

What are additional possible serious side effects of RITUXAN?

Tell your doctor right away about any side effect you experience. RITUXAN can cause serious side effects that can lead to death, including:

- **Serious Infections**: can happen during and after treatment and can lead to death. These infections may be bacterial, fungal, or viral. Symptoms can include fever; cold or flu symptoms; earache or headache; pain during urination; white patches in the mouth or throat; cuts or scrapes that are red, warm, swollen, or painful

Please see pages 57-65 and accompanying full Prescribing Information for RITUXAN and RITUXAN HYCELA, including their respective Medication Guides, for additional Important Safety Information.
Maintenance treatment for FL

RITUXAN® (rituximab) or RITUXAN HYCELA™ (rituximab/hyaluronidase human) may also be given as maintenance therapy for those patients who had a partial response or a complete response with their initial therapy of RITUXAN or RITUXAN HYCELA and chemotherapy. RITUXAN HYCELA can be prescribed alone, without chemotherapy, every 8 weeks for 12 doses during this phase of the journey. Your goal here is to help keep your disease in remission.

Important Information about RITUXAN HYCELA (cont’d)

What are possible side effects of RITUXAN HYCELA?

RITUXAN HYCELA can cause serious side effects, including:

- Tumor Lysis Syndrome (TLS): TLS is caused by the fast breakdown of cancer cells. TLS can cause you to have kidney failure, the need for dialysis treatment, and an abnormal heart rhythm. TLS can happen within 12 to 24 hours after an injection of RITUXAN HYCELA. Your healthcare provider may do blood tests to check you for TLS. Your healthcare provider may give you medicine to help prevent TLS. Tell your healthcare provider right away if you have any of the following signs or symptoms of TLS: nausea, vomiting, diarrhea, or lack of energy.

Your first dose will always be RITUXAN® (rituximab) with CHOP or CVP chemotherapy. If you were able to receive and tolerate at least one full dose of RITUXAN, you may receive RITUXAN HYCELA™ (rituximab/hyaluronidase human) with CHOP or CVP chemotherapy during future cycles of treatment.

As a maintenance therapy—RITUXAN or RITUXAN HYCELA may be prescribed by your healthcare provider by itself for FL for 12 doses when initial treatment with intravenous RITUXAN or RITUXAN HYCELA plus chemotherapy results in a partial or complete remission.

Please see pages 57-65 and accompanying full Prescribing Information for RITUXAN and RITUXAN HYCELA, including their respective Medication Guides, for additional Important Safety Information.
Treatment for relapsed or refractory FL

RITUXAN® (rituximab) or RITUXAN HYCELA™ (rituximab/hyaluronidase human) may also be given as therapy for those patients who relapsed after or were refractory to initial therapy. Your first dose will be RITUXAN. If you were able to receive and tolerate at least one full dose of RITUXAN, you may receive RITUXAN HYCELA during future cycles of treatment.

Important Safety Information about RITUXAN HYCELA (cont’d)

What are possible side effects of RITUXAN HYCELA?

RITUXAN HYCELA can cause serious side effects, including:

- Serious Infections: Serious infections can happen during and after treatment with RITUXAN HYCELA and can lead to death. Rituximab products can increase your risk of getting infections and can lower the ability of your immune system to fight infections. Types of serious infections that can happen with RITUXAN HYCELA include bacterial, fungal, and viral infections. After receiving RITUXAN HYCELA, some people have developed low levels of certain antibodies in their blood for a long period of time (longer than 11 months). Some of these people with low antibody levels developed infections. Tell your healthcare provider right away if you have any symptoms of infection: fever; cold symptoms, such as runny nose or sore throat that do not go away; flu symptoms, such as cough, tiredness, and body aches; earache or headache; pain during urination; white patches in the mouth or throat; cuts, scrapes, or incisions that are red, warm, swollen, or painful

Please see pages 57-65 and accompanying Full Prescribing Information for RITUXAN and RITUXAN HYCELA, including their respective Medication Guides, for additional Important Safety Information.

Your FL treatment

START HERE

Your first dose will always be RITUXAN® (rituximab). If you were able to receive and tolerate at least one full dose of RITUXAN, you may receive RITUXAN HYCELA™ (rituximab/hyaluronidase human) during future cycles of treatment.

Keep track of your initial therapy appointments here

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Your first RITUXAN infusion may take 4 to 6 hours.

Your RITUXAN HYCELA injections will usually take 5 minutes. Your healthcare provider should monitor you for side effects for at least 15 minutes after you receive RITUXAN HYCELA.

*Subsequent RITUXAN infusions could take 3-4 hours.

RITUXAN 1 cycle + RITUXAN or RITUXAN HYCELA Once a week 3 or 7 doses
Your first dose will always be RITUXAN® (rituximab) with CHOP chemotherapy or other anthracycline-based chemotherapy regimens. If you were able to receive and tolerate at least one full dose of RITUXAN, you may receive RITUXAN HYCELA™ (rituximab/hyaluronidase human) with CHOP chemotherapy or other anthracycline-based chemotherapy regimens during future cycles of treatment. The goal in using this combination of drugs is to keep your cancer from getting worse.

You will have up to 8 cycles, or rounds, of treatment. Each cycle will last 21 days. Treatment occurs on the first day of each cycle and is followed with time for rest and recovery. Most people will complete their treatment in about 6 months.

Important Safety Information about RITUXAN HYCELA (cont’d)

RITUXAN HYCELA can cause serious side effects, including:
- **Heart Problems:** RITUXAN HYCELA may cause chest pain, irregular heartbeats, and heart attack. Your healthcare provider may monitor your heart during and after treatment with RITUXAN HYCELA if you have symptoms of heart problems or have a history of heart problems. Tell your healthcare provider right away if you have chest pain or irregular heartbeats during treatment with RITUXAN HYCELA.
- **Kidney Problems:** RITUXAN HYCELA can cause severe kidney problems that can lead to death. Your healthcare provider should do blood tests to check how well your kidneys are working. Please see pages 57-65 and accompanying full Prescribing Information for RITUXAN and RITUXAN HYCELA, including their respective Medication Guides, for additional Important Safety Information.

Your first dose will always be RITUXAN® (rituximab) with CHOP or other anthracycline-based chemotherapy regimens. If you were able to receive and tolerate at least one full dose of RITUXAN, you may receive RITUXAN HYCELA™ (rituximab/hyaluronidase human) with CHOP or other anthracycline-based chemotherapy regimens during future cycles of treatment.

### RITUXAN 1 cycle

**RITUXAN or RITUXAN HYCELA**

**Every 21 days**

Up to 7 cycles

### Important Safety Information about RITUXAN HYCELA (cont’d)

What are possible side effects of RITUXAN HYCELA?

RITUXAN HYCELA can cause serious side effects, including:
- Stomach and serious bowel problems that can sometimes lead to death: Bowel problems, including blockage or tears in the bowel, can happen if you receive RITUXAN HYCELA with chemotherapy medicines. Tell your healthcare provider right away if you have severe stomach-area (abdomen) pain or repeated vomiting during treatment with RITUXAN HYCELA.

Your healthcare provider will stop treatment with RITUXAN HYCELA if you have severe, serious, or life-threatening side effects.

Please see pages 57-65 and accompanying full Prescribing Information for RITUXAN and RITUXAN HYCELA, including their respective Medication Guides, for additional Important Safety Information.
Your first dose will always be RITUXAN® (rituximab) with the chemotherapy medicines fludarabine and cyclophosphamide. If you were able to receive and tolerate at least one full dose of RITUXAN, you may receive RITUXAN HYCELA™ (rituximab/hyaluronidase human) with fludarabine and cyclophosphamide chemotherapy during future cycles of treatment. These drugs work together in different ways to fight cancer. The goal in using this combination of drugs is to keep your cancer from getting worse.

You will have 6 cycles, or rounds, of treatment. Each cycle will last 28 days. Treatment occurs on the first day of each cycle and is followed with time for rest and recovery.

Most people will complete their treatment in about 6 months.

Important Safety Information about RITUXAN HYCELA (cont’d)

What are possible side effects of RITUXAN HYCELA?

The most common side effects of RITUXAN HYCELA in people with:

- FLI: infections, low white blood cell count, nausea, constipation, cough, and tiredness
- DLBCL: infections, low white blood cell count, loss of hair, nausea, and low red blood cell count
- CLL: infections, low white blood cell count, nausea, low platelet count, fever, vomiting, and injection site redness

The most common side effects of RITUXAN are infusion reactions, chills, infections, body aches, tiredness, and low white blood cells.

Your first RITUXAN injection may take 4 to 6 hours.* Your RITUXAN HYCELA injections will usually take 7 minutes. Your healthcare provider should monitor you for side effects for at least 15 minutes after you receive RITUXAN HYCELA.

Keep track of your initial therapy appointments here

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Your first dose will always be RITUXAN® (rituximab) with the chemotherapy medicines fludarabine and cyclophosphamide. If you were able to receive and tolerate at least one full dose of RITUXAN, you may receive RITUXAN HYCELA® (rituximab/hyaluronidase human) with fludarabine and cyclophosphamide chemotherapy during future cycles of treatment.

| Your first RITUXAN injection may take 4 to 6 hours.* |
| Every 28 days |
| 5 cycles |

*Subsequent RITUXAN infusions could take 3-4 hours.

What are additional possible serious side effects of RITUXAN?

Tell your doctor right away about any side effect you experience. RITUXAN can cause serious side effects that can lead to death, including:

- **Heart Problems:** symptoms can include chest pain and irregular heartbeats that may require treatment. Your doctor may need to stop your treatment
- **Kidney Problems:** your doctor should do blood tests to check how well your kidneys are working
- **Stomach and Serious Bowel Problems:** can include blockage or tears in the bowel that can lead to death. Stomach area pain during treatment can be a symptom
- **Low Blood Cell Counts:** your blood cell counts may be monitored during treatment

The most common side effects of RITUXAN are infusion reactions, chills, infections, body aches, tiredness, and low white blood cells.

Please see pages 57-65 and accompanying full Prescribing Information for RITUXAN and RITUXAN HYCELA, including their respective Medication Guides, for additional Important Safety Information. 
Receiving your treatment

Additional Medications
Your doctor will give you medicines before your treatment with RITUXAN® (rituximab) or RITUXAN HYCELA™ (rituximab/hyaluronidase human). Medications commonly used before treatment include antihistamines, acetaminophen, and steroids.

If you have CLL, your doctor should prescribe medicines to help prevent certain infections during treatment and for up to 12 months following treatment with RITUXAN or RITUXAN HYCELA.

Important Safety Information about RITUXAN HYCELA

What is the most important information I should know about RITUXAN HYCELA?

RITUXAN HYCELA can cause serious side effects that can lead to death, including:

- Serious allergic reactions, and other severe reactions: Serious allergic reactions, and reactions due to release of certain substances by your body that can lead to death, can happen with rituximab products, including RITUXAN HYCELA.

Skin reactions at or near the injection site (local), including injection site reactions can happen with RITUXAN HYCELA. Symptoms at or near the injection site may include: pain, swelling, hardness, redness, bleeding, itching, and rash. These reactions sometimes happen more than 24 hours after an injection of RITUXAN HYCELA.

Tell your healthcare provider or get medical help right away if you get any of these symptoms during or after an injection of RITUXAN HYCELA: hives (red itchy welts) or rash; itching; swelling of your lips, tongue, throat, or face; sudden cough; shortness of breath, difficulty breathing, or wheezing; weakness; dizziness or feeling faint; palpitations (feeling like your heart is racing or fluttering); chest pain; fever; chills or shaking chills.

Please see pages 57-65 and accompanying full Prescribing Information for RITUXAN and RITUXAN HYCELA, including their respective Medication Guides, for additional Important Safety Information.

Receiving your treatment (cont’d)

How will I be given intravenous RITUXAN?
RITUXAN is given by infusion through a needle placed in a vein in your arm. Before your RITUXAN treatment, your doctor or nurse will ask you questions about your general health. Tell your doctor or nurse about any new symptoms. You will be monitored for side effects during your infusion.

How will I be given RITUXAN HYCELA?
Before each injection of RITUXAN HYCELA treatment, your doctor or nurse will ask you questions about your general health. Tell your doctor or nurse about any new symptoms. RITUXAN HYCELA is given as an approximately 5 to 7 minute subcutaneous injection at a clinic or infusion center. Subcutaneous injections are typically given with smaller needles than those used for intravenous infusions. You will receive your treatment as an injection under the skin in your abdomen. After receiving RITUXAN HYCELA, you will be monitored for at least 15 minutes to watch out for any side effects.

Important Safety Information about RITUXAN

RITUXAN can cause serious side effects that can lead to death, including infusion reactions. Infusion reactions are the most common side effect of RITUXAN treatment. Serious infusion reactions can happen during your infusion or within 24 hours after your infusion of RITUXAN. Symptoms can include hives, rash, itching, facial or oral swelling, sudden cough, shortness of breath, difficulty breathing, weakness, dizziness, feeling faint, racing heart, or chest pain. Tell your doctor or get medical help right away if you get any of these symptoms during or after an infusion of RITUXAN.

WHAT TO EXPECT
How much time does a treatment take?

The first infusion of RITUXAN® (rituximab) is given slowly
Your first dose will be an infusion of RITUXAN and may take 4 to 6 hours or more. If you have an infusion-related reaction, your infusion will be slowed or stopped.

Your subsequent RITUXAN treatments should take less time
Starting with the second treatment cycle, your RITUXAN infusions will generally take between 3 and 4 hours. For appropriate previously untreated FL and DLBCL patients, RITUXAN can be administered over 90 minutes after the first infusion. If you’ve received a full dose of RITUXAN and tolerated the full infusion, you may be given the option of receiving your treatment subcutaneously with RITUXAN HYCELA™ (rituximab/hyaluronidase human) for subsequent treatments.

Treatment with subcutaneous RITUXAN HYCELA should take even less time
RITUXAN HYCELA is given as an injection under the skin, in the abdomen over 5 or 7 minutes. Your doctor should monitor you for side effects for at least 15 minutes after you receive an injection of RITUXAN HYCELA.

The RITUXAN and RITUXAN HYCELA administration times do not include the amount of time required for chemotherapy administration.

Preparing for your treatment

Use this checklist before each time you receive treatment to help get you ready:

- Ask your doctor or nurse about your medicine
  - If you take any other medicines, remind your doctor or nurse. Do not start any new medications without talking to your doctor. Your doctor may give you special instructions that day
- Read the RITUXAN and RITUXAN HYCELA Medication Guides
  - Talk to your doctor if you have any questions about your treatment
- Arrange transportation
  - The medicines that are given to help reduce side effects such as fever and chills may make you drowsy or dizzy, so it is a good idea to have someone else drive you home after treatments
- Ask questions
  - Be sure to tell your doctor or nurse about any concerns you have before beginning your treatment
- Pack something to eat and drink: There are no special rules about what you should eat or drink before treatment. You may want to take some snacks or a packed meal.
- Pack something to do: Activities such as crossword puzzles or a book to read can help you pass the time.
Questions to ask your doctor

Before starting treatment, you may have questions that are important to ask. Remember, your doctor and other members of your healthcare team are the best sources of information. It’s a good idea to make a list of questions to ask at your next appointment.

It’s also a good idea to take along a family member or friend to help you keep track of the answers.

Here are some questions to consider asking:

- What kind and stage of disease do I have?
- What are my treatment options?
- What will my treatment schedule be?
- Am I healthy enough for RITUXAN® (rituximab) or RITUXAN HYCELA™ (rituximab/hyaluronidase human) plus chemotherapy?
- What are the risks and possible side effects of treatment?
- Where can I find information about support to help me pay for my treatment therapy?
- Do I need to take medication at home as well?
- Is there more I can do to make the most of my treatment?
- How will treatment with RITUXAN or RITUXAN HYCELA affect my lifestyle (working, traveling, etc)?

Learn more about RITUXAN at www.RITUXAN.com
Learn more about RITUXAN HYCELA at www.RITUXANHYCELA.com

Please see pages 57-65 and accompanying full Prescribing Information for RITUXAN and RITUXAN HYCELA, including their respective Medication Guides, for Important Safety Information.
Support for your journey
Support from Genentech

The Genentech BioOncology Co-pay Card
Genentech offers the Genentech BioOncology Co-pay Card that may help you with the out-of-pocket costs of RITUXAN® (rituximab) or RITUXAN HYCELA™ (rituximab/hyaluronidase human).*

* The Genentech BioOncology Co-pay Card is available only for commercially insured patients. Patients using Medicare, Medicaid or any other government funded program to pay for their medications are not eligible. It requires a valid, on-label prescription and cannot be combined with any other rebate/coupon, free trial or similar offer for the specified prescription. It is available only for a patient (or their guardian) who is 18 years or older. It is not valid for medications the patient receives for free or that are eligible to be reimbursed by private insurance plans or other health care or pharmaceutical assistance programs that reimburse the patient in whole or in part for the medication. It is valid only for Genentech products in the United States and Puerto Rico. The Genentech BioOncology Co-pay Card is not health insurance or a benefit plan. Please visit CopayAssistanceNow.com for the full list of terms and conditions.

Referrals to Independent Co-pay Assistance Foundations
If you need help with your co-pay for RITUXAN or RITUXAN HYCELA, Genentech Access Solutions can refer you to an independent co-pay assistance foundation.†

† Independent co-pay assistance foundations have their own rules for eligibility. We cannot guarantee a foundation will help you. We only can refer you to a foundation that supports your disease state. We do not endorse or show financial preference for any particular foundation. The foundations we refer you to are not the only ones that might be able to help you.

The Genentech® Access to Care Foundation (GATCF)
GATCF helps people who don’t have health insurance. It also helps people who have health insurance but have trouble paying for RITUXAN or RITUXAN HYCELA. If you qualify for GATCF, you could receive RITUXAN or RITUXAN HYCELA for free.

To learn more about how we can help, CALL 1-888-249-4918
VISIT www.genentech-access.com/RITUXAN/patients or www.genentech-access.com/RITUXANHYCELA/patients

Please see pages 57-65 and accompanying full Prescribing Information for RITUXAN and RITUXAN HYCELA, including their respective Medication Guides, for Important Safety Information.
Helpful resources

Many patient support groups offer helpful information about cancer. Some may also help you connect with a local support group. You can share your experiences and learn more about FL, DLBCL, or CLL. Many people find this helps them stay informed and stay positive.

Cancer organizations
American Cancer Society 1-800-ACS-2345 (1-800-227-2345) www.cancer.org
Cancer Care, Inc. 1-800-813-HOPE (1-800-813-4673) www.cancercare.org
National Cancer Institute 1-800-4-CANCER (1-800-422-6237) www.cancer.gov
National Comprehensive Cancer Network www.nccn.org/patients

Lymphoma organizations
The Leukemia & Lymphoma Society 1-800-555-4572 www.lls.org
Lymphoma Research Foundation 1-800-500-9976 www.lymphoma.org

Support organizations
Cancer Hope Network 1-877-HOPENET (1-877-467-3638) www.cancerhopenetwork.org
Cancer Support Community 1-888-793-WELL (1-888-793-9355) www.cancersupportcommunity.org
Patient Advocate Foundation 1-800-532-5274 www.patientadvocate.org

Genentech and Biogen do not control or endorse third-party organizations. The information provided by Genentech, Biogen, or these organizations is meant for informational purposes only. It is not meant to replace your doctor’s medical advice.

Did your healthcare team help you with your RITUXAN® (rituximab) or RITUXAN HYCELA™ (rituximab/hyaluronidase human) treatment? If so, why not share your gratitude with the tear-out card below?

THANK YOU FOR CARING!

Dear _______________________

Thank you for your care.

Sincerely,

Please see pages 57-65 and accompanying full Prescribing Information for RITUXAN and RITUXAN HYCELA, including their respective Medication Guides, for Important Safety Information.
Important Safety Information about RITUXAN

What is the most important information I should know about RITUXAN?

Tell your doctor right away about any side effect you experience. RITUXAN can cause serious side effects that can lead to death, including:

- **Infusion Reactions:** may occur during or within 24 hours of your infusion. Your doctor should give you medicines before your treatment. Symptoms can include hives, rash, itching, facial or oral swelling, sudden cough, shortness of breath, difficulty breathing, weakness, dizziness, feeling faint, racing heart, or chest pain

- **Severe Skin and Mouth Reactions:** symptoms can include painful sores, ulcers, or blisters on your skin, lips or mouth; peeling skin; rash; or pustules

- **Hepatitis B Virus (HBV) Reactivation:** may cause serious liver problems including liver failure and death. If you have had hepatitis B or are a carrier of HBV, receiving RITUXAN could cause the virus to become an active infection again. You should not receive RITUXAN if you have active HBV liver disease. Your doctor will do blood tests to check for HBV infection prior to treatment and will monitor you during and for several months following your treatment.

- **Progressive Multifocal Leukoencephalopathy (PML):** a rare, serious brain infection that can lead to severe disability and death and for which there is no known prevention, treatment, or cure. Symptoms can include difficulty thinking, loss of balance, changes in speech or walking, weakness on one side of your body, or blurred or lost vision

Please see pages 58-59 and accompanying RITUXAN full Prescribing Information, including Medication Guide, for additional Important Safety Information.
Important Safety Information about RITUXAN (cont’d)

What are the additional possible serious side effects of RITUXAN?

Tell your doctor right away about any side effect you experience. RITUXAN can cause serious side effects that can lead to death, including:

- **Tumor Lysis Syndrome (TLS):** may cause kidney failure and the need for dialysis treatment, abnormal heart rhythm, and can lead to death. Your doctor may give you medicines before your treatment to help prevent TLS.

- **Serious Infections:** can happen during and after treatment and can lead to death. These infections may be bacterial, fungal, or viral. Symptoms can include fever; cold or flu symptoms; earache or headache; pain during urination; white patches in the mouth or throat; cuts or scrapes that are red, warm, swollen, or painful.

- **Heart Problems:** symptoms can include chest pain and irregular heartbeats that may require treatment. Your doctor may need to stop your treatment.

- **Kidney Problems:** your doctor should do blood tests to check how well your kidneys are working.

- **Stomach and Serious Bowel Problems:** can include blockage or tears in the bowel that can lead to death. Stomach area pain during treatment can be a symptom.

- **Low Blood Cell Counts:** your blood cell counts may be monitored during treatment.

The most common side effects of RITUXAN are infusion reactions, chills, infections, body aches, tiredness, and low white blood cells.

Other side effects with RITUXAN include:

- Aching joints during or within hours of receiving an infusion
- More frequent upper respiratory tract infections

Tell your doctor if you are pregnant, plan to become pregnant, or are breastfeeding. It is not known if RITUXAN may harm your unborn baby or pass into your breast milk. Women should use birth control while using RITUXAN and for 12 months after treatment.

Tell your doctor about any side effect that bothers you or that does not go away. These are not all of the possible side effects of RITUXAN. For more information, ask your doctor or pharmacist.

Please see the accompanying RITUXAN full Prescribing Information, including the Medication Guide, for additional Important Safety Information. You can also download it at www.RITUXAN.com.

You may report side effects to the FDA at (800) FDA-1088 or www.fda.gov/medwatch. You may also report side effects to Genentech at (888) 835-2555.
Important Safety Information about RITUXAN HYCELA

What is the most important information I should know about RITUXAN HYCELA?

RITUXAN HYCELA can cause serious side effects that can lead to death, including:

- **Severe skin and mouth reactions:** Tell your healthcare provider or get medical help right away if you get any of these symptoms at any time during your treatment with RITUXAN HYCELA: painful sores or ulcers on your skin, lips, or in your mouth; blistering; peeling skin; rash or pustules

- **Hepatitis B virus (HBV) reactivation:** Before you receive RITUXAN HYCELA, your doctor will do blood tests to check for HBV infection. If you have had hepatitis B or are a carrier of hepatitis B virus, receiving RITUXAN HYCELA could cause the virus to become an active infection again. Hepatitis B reactivation may cause serious liver problems including liver failure and death. Your healthcare provider will monitor you for hepatitis B infection during and for several months after you stop receiving RITUXAN HYCELA. Tell your healthcare provider right away if you get worsening tiredness, or yellowing of your skin or white part of your eyes during treatment with RITUXAN HYCELA.

- **Progressive multifocal leukoencephalopathy (PML):** PML is a rare, serious brain infection caused by a virus that can happen in people who receive RITUXAN HYCELA. People with weakened immune systems can get PML. PML can result in death or severe disability. There is no known treatment, prevention, or cure for PML. Tell your healthcare provider right away if you have any new or worsening symptoms or if anyone close to you notices these symptoms: confusion; dizziness or loss of balance; difficulty walking or talking; decreased strength or weakness on one side of your body; vision problems, such as blurred or loss of vision.

- **Serious allergic reactions and other severe reactions:**
  - Serious allergic reactions, and reactions due to release of certain substances by your body that can lead to death, can happen with rituximab products, including RITUXAN HYCELA.
  - Skin reactions at or near the injection site (local), including injection site reactions can happen with RITUXAN HYCELA. Symptoms at or near the injection site may include: pain, swelling, hardness, redness, bleeding, itching, and rash. These reactions sometimes happen more than 24 hours after an injection of RITUXAN HYCELA.
  - Tell your healthcare provider or get medical help right away if you get any of these symptoms during or after an injection of RITUXAN HYCELA: hives (red itchy welts) or rash; itching; swelling of your lips, tongue, throat, or face; sudden cough; shortness of breath, difficulty breathing, or wheezing; weakness; dizziness or feeling faint; palpitations (feeling like your heart is racing or fluttering); chest pain; fever; chills or shaking chills.

Please see pages 61-65 and accompanying RITUXAN HYCELA full Prescribing Information, including Medication Guide, for additional Important Safety Information.
What are possible side effects of RITUXAN HYCELA?

RITUXAN HYCELA can cause serious side effects, including:

- **Tumor Lysis Syndrome (TLS):** TLS is caused by the fast breakdown of cancer cells. TLS can cause you to have kidney failure, the need for dialysis treatment, and an abnormal heart rhythm. TLS can happen within 12 to 24 hours after an injection of RITUXAN HYCELA. Your healthcare provider may do blood tests to check you for TLS. Your healthcare provider may give you medicine to help prevent TLS. Tell your healthcare provider right away if you have any of the following signs or symptoms of TLS: nausea, vomiting, diarrhea, or lack of energy.

- **Serious Infections:** Serious infections can happen during and after treatment with RITUXAN HYCELA and can lead to death. Rituximab products can increase your risk of getting infections and can lower the ability of your immune system to fight infections. Types of serious infections that can happen with RITUXAN HYCELA include bacterial, fungal, and viral infections. After receiving RITUXAN HYCELA, some people have developed low levels of certain antibodies in their blood for a long period of time (longer than 11 months). Some of these people with low antibody levels developed infections. Tell your healthcare professional right away if you have any symptoms of infection: fever; cold symptoms, such as runny nose or sore throat that do not go away; flu symptoms, such as cough, tiredness, and body aches; earache or headache; pain during urination; white patches in the mouth or throat; cuts, scrapes, or incisions that are red, warm, swollen, or painful.

- **Heart Problems:** RITUXAN HYCELA may cause chest pain, irregular heartbeats, and heart attack. Your healthcare provider may monitor your heart during and after treatment with RITUXAN HYCELA if you have symptoms of heart problems or have a history of heart problems. Tell your healthcare provider right away if you have chest pain or irregular heartbeats during treatment with RITUXAN HYCELA.

- **Kidney Problems:** RITUXAN HYCELA can cause severe kidney problems that can lead to death. Your healthcare provider should do blood tests to check how well your kidneys are working.

- **Stomach and serious bowel problems that can sometimes lead to death:** Bowel problems, including blockage or tears in the bowel, can happen if you receive RITUXAN HYCELA with chemotherapy medicines. Tell your healthcare provider right away if you have severe stomach-area (abdomen) pain or repeated vomiting during treatment with RITUXAN HYCELA.

Your healthcare professional will stop treatment with RITUXAN HYCELA if you have severe, serious, or life-threatening side effects.

The most common side effects of RITUXAN HYCELA in people with:

- **FL:** infections, low white blood cell count, nausea, constipation, cough, and tiredness
- **DLBCL:** infections, low white blood cell count, loss of hair, nausea, and low red blood cell count
- **CLL:** infections, low white blood cell count, nausea, low platelet count, fever, vomiting, and injection site redness

Please see pages 63-65 and accompanying RITUXAN HYCELA full Prescribing Information, including Medication Guide, for additional Important Safety Information.
Important Safety Information about RITUXAN HYCELA (cont’d)

Additional Safety Information
Before receiving RITUXAN HYCELA, tell your doctor about all of your medical conditions, including if you:

- Have had a severe reaction to a rituximab-containing product or RITUXAN HYCELA
- Have had a recent vaccination or are scheduled to receive vaccinations. You should not receive certain vaccines before or during treatment with RITUXAN HYCELA
- Are pregnant, plan to become pregnant, are breastfeeding, or plan to breastfeed. Talk to your doctor about the risks to your unborn baby if you receive RITUXAN HYCELA during pregnancy. Females who are able to become pregnant should use effective birth control during treatment with RITUXAN HYCELA and for 12 months after the last dose of a rituximab-containing product, such as RITUXAN HYCELA. It is not known if RITUXAN HYCELA passes into your breast milk. Do not breastfeed during treatment and for at least 6 months after your last dose of RITUXAN HYCELA

These are not all of the possible side effects with RITUXAN HYCELA. Call your doctor for medical advice about side effects.

Please see the accompanying RITUXAN HYCELA full Prescribing Information, including Medication Guide, for additional Important Safety Information.

You may report side effects to the FDA at (800) FDA-1088 or www.fda.gov/medwatch. You may also report side effects to Genentech at (888) 835-2555.

Remember to tell your healthcare team exactly how you feel. This will allow them to take the proper actions to help you.
For more information, visit www.RITUXAN.com and www.RITUXANHYCELA.com or call Genentech’s center dedicated to getting patients and caregivers to the right resource. (877) GENENTECH • (877) 436-3683 • 6 AM - 5 PM PT M-F

Please see pages 57-65 and accompanying full Prescribing Information for RITUXAN and RITUXAN HYCELA, including their respective Medication Guides, for Important Safety Information.

Images in this brochure do not depict actual patients or healthcare providers.
WARNING: FATAL INFUSION REACTIONS, SEVERE MUCOCUTANEOUS REACTIONS, HEPATITIS B VIRUS REACTIVATION and PROGRESSIVE MULTIFOcal LEUKOENCEPHALOPATHY
See full prescribing information for complete boxed warning.

- Fatal infusion reactions within 24 hours of Rituxan infusion; approximately 80% of fatal reactions occurred with first infusion. Monitor patients and discontinue Rituxan infusion for severe reactions (5.1).
- Severe mucocutaneous reactions, some with fatal outcomes (5.2).
- Hepatitis B virus (HBV) reactivation, in some cases resulting in fulminant hepatitis, hepatic failure, and death (5.3).
- Progressive multifocal leukoencephalopathy (PML) resulting in death (5.4).

RECENT MAJOR CHANGES

Rituxan® (rituximab) is a CD20-directed cytolytic antibody indicated for the treatment of patients with:
- Non-Hodgkin’s Lymphoma (NHL) (1.1)
- Chronic Lymphocytic Leukemia (CLL) (1.2)
- Rheumatoid Arthritis (RA) in combination with methotrexate in adult patients with moderately-to severely-active RA who have inadequate response to one or more TNF antagonist therapies (1.3)
- Granulomatosis with Polyangiitis (GPA) (Wegener’s Granulomatosis) and Microscopic Polyangiitis (MPA) in adult patients in combination with glucocorticoids (1.4)

Limitations of Use: Rituxan is not recommended for use in patients with severe, active infections (1.5).

INDICATIONS AND USAGE

Rituxan® (rituximab) is a CD20-directed cytolytic antibody indicated for:
- NHL (1.1)
- CLL (1.2)
- RA (1.3)
- GPA (1.4)

The dose for RA in combination with methotrexate is two-1000 mg intravenous infusions separated by 2 weeks (one course) every 24 weeks or based on clinical evaluation, but not sooner than every 16 weeks. Methylprednisolone 100 mg intravenous or equivalent glucocorticoid is recommended 30 minutes prior to each infusion (2.5).

The dose for GPA and MPA in combination with glucocorticoids is 375 mg/m² once weekly for 4 weeks (2.6).

DOSAGE FORMS AND STRENGTHS

Injection: 100 mg/10 mL and 500 mg/50 mL solution in a single-use vial

CONTRAINDICATIONS

None.

WARNINGS AND PRECAUTIONS

- Tumor lysis syndrome: Administer aggressive intravenous hydration, anti-hyperuricemic agents, monitor renal function (5.5).
- Infections: Withhold Rituxan and institute appropriate anti-infective therapy (5.6).
- Cardiac arrhythmias and angina: Discontinue infusions in case of serious or life-threatening events (5.7).
- Bowel obstruction and perforation: Consider and evaluate for abdominal pain, vomiting, or related symptoms (5.9).
- Live virus vaccines: Do not administer live virus vaccines prior to or during Rituxan (5.10).
- Cytopenias: Monitor blood counts at regular intervals (5.11, 6.1).

ADVERSE REACTIONS

Most common adverse reactions in clinical trials were:
- NHL (≥25%): infusion reactions, fever, lymphopenia, chills, infection and asthma (6.1).
- CLL (≥25%): infusion reactions and neutropenia (6.1).
- RA (≥10%): upper respiratory tract infection, nasopharyngitis, urinary tract infection, and bronchitis (other important adverse reactions include infusion reactions, serious infections, and cardiovascular events) (6.2).
- GPA and MPA (≥15 %): infections, nausea, diarrhoea, headache, muscle spasms, anemia, peripheral edema (other important adverse reactions include infusion reactions) (6.3).

To report SUSPECTED ADVERSE REACTIONS, contact Genentech at 1-888-835-2555 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

Renal toxicity when used in combination with cisplatin (5.8).

USE IN SPECIFIC POPULATIONS

- Pregnancy: Limited human data; B-cell lymphocytopenia occurred in infants exposed in utero (8.1).
- Geriatric Use: In CLL patients older than 70 years of age, exploratory analyses suggest no benefit with the addition of Rituxan to FC (8.5).

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.
FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING: FATAL INFUSION REACTIONS, SEVERE MUCOCUTANEOUS REACTIONS, HEPATITIS B VIRUS REACTIVATION and PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY (PML)

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*Sections or subsections omitted from the full prescribing information are not listed.
FULL PRESCRIBING INFORMATION

WARNING: FATAL INFUSION REACTIONS, SEVERE MUCOCUTANEOUS REACTIONS, HEPATITIS B VIRUS REACTIVATION and PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY

Infusion Reactions
Rituxan administration can result in serious, including fatal infusion reactions. Deaths within 24 hours of Rituxan infusion have occurred. Approximately 80% of fatal infusion reactions occurred in association with the first infusion. Monitor patients closely. Discontinue Rituxan infusion for severe reactions and provide medical treatment for Grade 3 or 4 infusion reactions [see Warnings and Precautions (5.1), Adverse Reactions (6.1)].

Severe Mucocutaneous Reactions
Severe, including fatal, mucocutaneous reactions can occur in patients receiving Rituxan [see Warnings and Precautions (5.2), Adverse Reactions (6)].

Hepatitis B Virus (HBV) Reactivation
HBV reactivation can occur in patients treated with Rituxan, in some cases resulting in fulminant hepatitis, hepatic failure, and death. Screen all patients for HBV infection before treatment initiation, and monitor patients during and after treatment with Rituxan. Discontinue Rituxan and concomitant medications in the event of HBV reactivation [see Warnings and Precautions (5.3), Adverse Reactions (6)].

Progressive Multifocal Leukoencephalopathy (PML), including fatal PML, can occur in patients receiving Rituxan [see Warnings and Precautions (5.4), Adverse Reactions (6)].

1 INDICATIONS AND USAGE
1.1 Non–Hodgkin’s Lymphoma (NHL)
Rituxan® (rituximab) is indicated for the treatment of patients with:

- Relapsed or refractory, low-grade or follicular, CD20-positive, B-cell NHL as a single agent
- Previously untreated follicular, CD20-positive, B-cell NHL in combination with first line chemotherapy and, in patients achieving a complete or partial response to Rituxan in combination with chemotherapy, as single-agent maintenance therapy.
- Non-progressing (including stable disease), low-grade, CD20-positive, B-cell NHL as a single agent after first-line CVP chemotherapy
- Previously untreated diffuse large B-cell, CD20-positive NHL in combination with CHOP or other anthracycline-based chemotherapy regimens

1.2 Chronic Lymphocytic Leukemia (CLL)
Rituxan® (rituximab) is indicated, in combination with fludarabine and cyclophosphamide (FC), for the treatment of patients with previously untreated and previously treated CD20-positive CLL.

1.3 Rheumatoid Arthritis (RA)
Rituxan® (rituximab) in combination with methotrexate is indicated for the treatment of adult patients with moderately- to severely- active rheumatoid arthritis who have had an inadequate response to one or more TNF antagonist therapies.

1.4 Granulomatosis with Polyangiitis (GPA) (Wegener’s Granulomatosis) and Microscopic Polyangiitis (MPA)
Rituxan® (rituximab), in combination with glucocorticoids, is indicated for the treatment of adult patients with Granulomatosis with Polyangiitis (GPA) (Wegener’s Granulomatosis) and Microscopic Polyangiitis (MPA).

1.5 Limitations of Use
Rituxan is not recommended for use in patients with severe, active infections.
2  DOSAGE AND ADMINISTRATION

2.1  Administration

Administer only as an Intravenous Infusion [see Dosage and Administration (2.7)].
Do not administer as an intravenous push or bolus.
Premedicate before each infusion [see Dosage and Administration (2.7)].
Rituxan should only be administered by a healthcare professional with appropriate medical support to manage severe infusion reactions that can be fatal if they occur [see Warnings and Precautions (5.1)].

- **First Infusion**: Initiate infusion at a rate of 50 mg/hr. In the absence of infusion toxicity, increase infusion rate by 50 mg/hr increments every 30 minutes, to a maximum of 400 mg/hr.

- **Subsequent Infusions**:  
  *Standard Infusion*: Initiate infusion at a rate of 100 mg/hr. In the absence of infusion toxicity, increase rate by 100 mg/hr increments at 30-minute intervals, to a maximum of 400 mg/hr.  
  *For previously untreated follicular NHL and DLBCL patients*:  
  If patients did not experience a Grade 3 or 4 infusion related adverse event during Cycle 1, a 90-minute infusion can be administered in Cycle 2 with a glucocorticoid-containing chemotherapy regimen.  
  Initiate at a rate of 20% of the total dose given in the first 30 minutes and the remaining 80% of the total dose given over the next 60 minutes. If the 90-minute infusion is tolerated in Cycle 2, the same rate can be used when administering the remainder of the treatment regimen (through Cycle 6 or 8).  
  Patients who have clinically significant cardiovascular disease or who have a circulating lymphocyte count ≥5000/mm³ before Cycle 2 should not be administered the 90-minute infusion [see Clinical Studies (14.4)].

- Interrupt the infusion or slow the infusion rate for infusion reactions [see Boxed Warning, Warnings and Precautions (5.1)]. Continue the infusion at one-half the previous rate upon improvement of symptoms.

2.2  Recommended Dose for Non-Hodgkin’s Lymphoma (NHL)
The recommended dose is 375 mg/m² as an intravenous infusion according to the following schedules:

- **Relapsed or Refractory, Low-Grade or Follicular, CD20-Positive, B-Cell NHL**  
  Administer once weekly for 4 or 8 doses.

- **Retreatment for Relapsed or Refractory, Low-Grade or Follicular, CD20-Positive, B-Cell NHL**  
  Administer once weekly for 4 doses.

- **Previously Untreated, Follicular, CD20-Positive, B-Cell NHL**  
  Administer on Day 1 of each cycle of chemotherapy, for up to 8 doses. In patients with complete or partial response, initiate Rituxan maintenance eight weeks following completion of Rituxan in combination with chemotherapy. Administer Rituxan as a single-agent every 8 weeks for 12 doses.

- **Non-progressing, Low-Grade, CD20-Positive, B-cell NHL, after first-line CVP chemotherapy**  
  Following completion of 6–8 cycles of CVP chemotherapy, administer once weekly for 4 doses at 6-month intervals to a maximum of 16 doses.

- **Diffuse Large B-Cell NHL**  
  Administer on Day 1 of each cycle of chemotherapy for up to 8 infusions.

2.3  Recommended Dose for Chronic Lymphocytic Leukemia (CLL)
The recommended dose is:

- 375 mg/m² the day prior to the initiation of FC chemotherapy, then 500 mg/m² on Day 1 of cycles 2–6 (every 28 days).
2.4 **Recommended Dose as a Component of Zevalin® for treatment of NHL**

- Infuse rituximab 250 mg/m² within 4 hours prior to the administration of Indium-111-(In-111-) Zevalin and within 4 hours prior to the administration of Yttrium-90- (Y-90-) Zevalin.
- Administer Rituxan and In-111-Zevalin 7–9 days prior to Rituxan and Y-90- Zevalin.
- Refer to the Zevalin package insert for full prescribing information regarding the Zevalin therapeutic regimen.

2.5 **Recommended Dose for Rheumatoid Arthritis (RA)**

- Administer Rituxan as two-1000 mg intravenous infusions separated by 2 weeks.
- Glucocorticoids administered as methylprednisolone 100 mg intravenous or its equivalent 30 minutes prior to each infusion are recommended to reduce the incidence and severity of infusion reactions.
- Subsequent courses should be administered every 24 weeks or based on clinical evaluation, but not sooner than every 16 weeks.
- Rituxan is given in combination with methotrexate.

2.6 **Recommended Dose for Granulomatosis with Polyangiitis (GPA) (Wegener’s Granulomatosis) and Microscopic Polyangiitis (MPA)**

- Administer Rituxan as a 375 mg/m² intravenous infusion once weekly for 4 weeks.
- Glucocorticoids administered as methylprednisolone 1000 mg intravenously per day for 1 to 3 days followed by oral prednisone 1 mg/kg/day (not to exceed 80 mg/day and tapered per clinical need) are recommended to treat severe vasculitis symptoms. This regimen should begin within 14 days prior to or with the initiation of Rituxan and may continue during and after the 4 week course of Rituximab treatment.
- Safety and efficacy of treatment with subsequent courses of Rituxan have not been established [see Warnings and Precautions (5.14)].

2.7 **Recommended Concomitant Medications**

Premedicate before each infusion with acetaminophen and an antihistamine. For patients administered Rituxan according to the 90-minute infusion rate, the glucocorticoid component of their chemotherapy regimen should be administered prior to infusion [see Clinical Studies (14.4)].

For RA patients, methylprednisolone 100 mg intravenously or its equivalent is recommended 30 minutes prior to each infusion.

For GPA and MPA patients, glucocorticoids are given in combination with Rituxan [see Dosage and Administration (2.6)].

Pneumocystis jiroveci pneumonia (PCP) and anti-herpetic viral prophylaxis is recommended for patients with CLL during treatment and for up to 12 months following treatment as appropriate. PCP prophylaxis is also recommended for patients with GPA and MPA during treatment and for at least 6 months following the last Rituxan infusion.

2.8 **Preparation for Administration**

Use appropriate aseptic technique. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration. Do not use vial if particulates or discoloration is present. Withdraw the necessary amount of Rituxan and dilute to a final concentration of 1 mg/mL to 4 mg/mL in an infusion bag containing either 0.9% Sodium Chloride, USP, or 5% Dextrose in Water, USP. Gently invert the bag to mix the solution. Do not mix or dilute with other drugs. Discard any unused portion left in the vial.

Rituxan solutions for infusion may be stored at 2°C–8°C (36°F–46°F) for 24 hours. Rituxan solutions for infusion have been shown to be stable for an additional 24 hours at room temperature. However, since Rituxan solutions do not contain a preservative, diluted solutions should be stored refrigerated (2°C–8°C). No incompatibilities between Rituxan and polyvinylchloride or polyethylene bags have been observed.
3 DOSAGE FORMS AND STRENGTHS
Injection:
- 100 mg/10 mL in a single-use vial
- 500 mg/50 mL in a single-use vial

4 CONTRAINDICATIONS
None.

5 WARNINGS AND PRECAUTIONS
5.1 Infusion Reactions
Rituxan can cause severe, including fatal, infusion reactions. Severe reactions typically occurred during the first infusion with time to onset of 30–120 minutes. Rituxan-induced infusion reactions and sequelae include urticaria, hypotension, angioedema, hypoxia, bronchospasm, pulmonary infiltrates, acute respiratory distress syndrome, myocardial infarction, ventricular fibrillation, cardiogenic shock, anaphylactoid events, or death.

 Premedicate patients with an antihistamine and acetaminophen prior to dosing. For RA patients, methylprednisolone 100 mg intravenously or its equivalent is recommended 30 minutes prior to each infusion. Institute medical management (e.g. glucocorticoids, epinephrine, bronchodilators, or oxygen) for infusion reactions as needed. Depending on the severity of the infusion reaction and the required interventions, temporarily or permanently discontinue Rituxan. Resume infusion at a minimum 50% reduction in rate after symptoms have resolved. Closely monitor the following patients: those with pre-existing cardiac or pulmonary conditions, those who experienced prior cardiopulmonary adverse reactions, and those with high numbers of circulating malignant cells (≥25,000/mm³). [See Boxed Warning, Warnings and Precautions (5.7), Adverse Reactions (6.1)].

5.2 Severe Mucocutaneous Reactions
Mucocutaneous reactions, some with fatal outcome, can occur in patients treated with Rituxan. These reactions include paraneoplastic pemphigus, Stevens-Johnson syndrome, lichenoid dermatitis, vesiculobullous dermatitis, and toxic epidermal necrolysis. The onset of these reactions has been variable and includes reports with onset on the first day of Rituxan exposure. Discontinue Rituxan in patients who experience a severe mucocutaneous reaction. The safety of readministration of Rituxan to patients with severe mucocutaneous reactions has not been determined. [See Boxed Warning, Adverse Reactions (6)].

5.3 Hepatitis B Virus Reactivation
Hepatitis B virus (HBV) reactivation, in some cases resulting in fulminant hepatitis, hepatic failure and death, can occur in patients treated with drugs classified as CD20-directed cytolytic antibodies, including Rituxan. Cases have been reported in patients who are hepatitis B surface antigen (HBsAg) positive and also in patients who are HBsAg negative but are hepatitis B core antibody (anti-HBc) positive. Reactivation also has occurred in patients who appear to have resolved hepatitis B infection (i.e., HBsAg negative, anti-HBc positive and hepatitis B surface antibody [anti-HBs] positive).

 HBV reactivation is defined as an abrupt increase in HBV replication manifesting as a rapid increase in serum HBV DNA level or detection of HBsAg in a person who was previously HBsAg negative and anti-HBc positive. Reactivation of HBV replication is often followed by hepatitis, i.e., increase in transaminase levels. In severe cases increase in bilirubin levels, liver failure, and death can occur.

 Screen all patients for HBV infection by measuring HBsAg and anti-HBc before initiating treatment with Rituxan. For patients who show evidence of prior hepatitis B infection (HBsAg positive [regardless of antibody status] or HBsAg negative but anti-HBc positive), consult with physicians with expertise in managing hepatitis B regarding monitoring and consideration for HBV antiviral therapy before and/or during Rituxan treatment.
Monitor patients with evidence of current or prior HBV infection for clinical and laboratory signs of hepatitis or HBV reactivation during and for several months following Rituxan therapy. HBV reactivation has been reported up to 24 months following completion of Rituxan therapy.

In patients who develop reactivation of HBV while on Rituxan, immediately discontinue Rituxan and any concomitant chemotherapy, and institute appropriate treatment. Insufficient data exist regarding the safety of resuming Rituxan in patients who develop HBV reactivation. Resumption of Rituxan in patients whose HBV reactivation resolves should be discussed with physicians with expertise in managing hepatitis B. [See Boxed Warning, Adverse Reactions (6)]

5.4 Progressive Multifocal Leukoencephalopathy (PML)
JC virus infection resulting in PML and death can occur in Rituxan-treated patients with hematologic malignancies or with autoimmune diseases. The majority of patients with hematologic malignancies diagnosed with PML received Rituxan in combination with chemotherapy or as part of a hematopoietic stem cell transplant. The patients with autoimmune diseases had prior or concurrent immunosuppressive therapy. Most cases of PML were diagnosed within 12 months of their last infusion of Rituxan.

Consider the diagnosis of PML in any patient presenting with new-onset neurologic manifestations. Evaluation of PML includes, but is not limited to, consultation with a neurologist, brain MRI, and lumbar puncture. Discontinue Rituxan and consider discontinuation or reduction of any concomitant chemotherapy or immunosuppressive therapy in patients who develop PML. [See Boxed Warning, Adverse Reactions (6)].

5.5 Tumor Lysis Syndrome (TLS)
Acute renal failure, hyperkalemia, hypocalcemia, hyperuricemia, or hyperphosphatemia from tumor lysis, some fatal, can occur within 12–24 hours after the first infusion of Rituxan in patients with NHL. A high number of circulating malignant cells (≥25,000/mm³) or high tumor burden, confers a greater risk of TLS.

Administer aggressive intravenous hydration and anti-hyperuricemic therapy in patients at high risk for TLS. Correct electrolyte abnormalities, monitor renal function and fluid balance, and administer supportive care, including dialysis as indicated. [See Warnings and Precautions (5.8), Adverse Reactions (6)].

5.6 Infections
Serious, including fatal, bacterial, fungal, and new or reactivated viral infections can occur during and following the completion of Rituxan-based therapy. Infections have been reported in some patients with prolonged hypogammaglobulinemia (defined as hypogammaglobulinemia >11 months after rituximab exposure). New or reactivated viral infections included cytomegalovirus, herpes simplex virus, parvovirus B19, varicella zoster virus, West Nile virus, and hepatitis B and C. Discontinue Rituxan for serious infections and institute appropriate anti-infective therapy. [See Adverse Reactions (6, 6.1)].

5.7 Cardiovascular
Discontinue infusions for serious or life-threatening cardiac arrhythmias. Perform cardiac monitoring during and after all infusions of Rituxan for patients who develop clinically significant arrhythmias, or who have a history of arrhythmia or angina. [See Adverse Reactions (6)].

5.8 Renal
Severe, including fatal, renal toxicity can occur after Rituxan administration in patients with NHL. Renal toxicity has occurred in patients who experience tumor lysis syndrome and in patients with NHL administered concomitant cisplatin therapy during clinical trials. The combination of cisplatin and Rituxan is not an approved treatment regimen. Monitor closely for signs of renal failure and discontinue Rituxan in patients with a rising serum creatinine or oliguria. [See Warnings and Precautions (5.5)].

5.9 Bowel Obstruction and Perforation
Abdominal pain, bowel obstruction and perforation, in some cases leading to death, can occur in patients receiving Rituxan in combination with chemotherapy. In postmarketing reports, the mean
time to documented gastrointestinal perforation was 6 (range 1–77) days in patients with NHL. Evaluate if symptoms of obstruction such as abdominal pain or repeated vomiting occur. [See Adverse Reactions (6)].

5.10 Immunization

The safety of immunization with live viral vaccines following Rituxan therapy has not been studied and vaccination with live virus vaccines is not recommended.

For RA patients, physicians should follow current immunization guidelines and administer non-live vaccines at least 4 weeks prior to a course of Rituxan.

The effect of Rituxan on immune responses was assessed in a randomized, controlled study in patients with RA treated with Rituxan and methotrexate (MTX) compared to patients treated with MTX alone.

A response to pneumococcal vaccination (a T-cell independent antigen) as measured by an increase in antibody titers to at least 6 of 12 serotypes was lower in patients treated with Rituxan plus MTX as compared to patients treated with MTX alone (19% vs. 61%). A lower proportion of patients in the Rituxan plus MTX group developed detectable levels of anti-keyhole limpet hemocyanin antibodies (a novel protein antigen) after vaccination compared to patients on MTX alone (47% vs. 93%).

A positive response to tetanus toxoid vaccine (a T-cell dependent antigen with existing immunity) was similar in patients treated with Rituxan plus MTX compared to patients on MTX alone (39% vs. 42%). The proportion of patients maintaining a positive Candida skin test (to evaluate delayed type hypersensitivity) was also similar (77% of patients on Rituxan plus MTX vs. 70% of patients on MTX alone).

Most patients in the Rituxan-treated group had B-cell counts below the lower limit of normal at the time of immunization. The clinical implications of these findings are not known.

5.11 Laboratory Monitoring

In patients with lymphoid malignancies, during treatment with Rituxan monotherapy, obtain complete blood counts (CBC) and platelet counts prior to each Rituxan course. During treatment with Rituxan and chemotherapy, obtain CBC and platelet counts at weekly to monthly intervals and more frequently in patients who develop cytopenias [See Adverse Reactions (6.1)]. In patients with RA, GPA or MPA, obtain CBC and platelet counts at two to four month intervals during Rituxan therapy. The duration of cytopenias caused by Rituxan can extend months beyond the treatment period.

5.12 Concomitant Use with Biologic Agents and DMARDs other than Methotrexate in RA, GPA and MPA

Limited data are available on the safety of the use of biologic agents or DMARDs other than methotrexate in RA patients exhibiting peripheral B-cell depletion following treatment with rituximab. Observe patients closely for signs of infection if biologic agents and/or DMARDs are used concomitantly. Use of concomitant immunosuppressants other than corticosteroids has not been studied in GPA or MPA patients exhibiting peripheral B-cell depletion following treatment with Rituxan.

5.13 Use in RA Patients Who Have Not Had Prior Inadequate Response to Tumor Necrosis Factor (TNF) Antagonists

While the efficacy of Rituxan was supported in four controlled trials in patients with RA with prior inadequate responses to non-biologic DMARDs, and in a controlled trial in MTX-naïve patients, a favorable risk-benefit relationship has not been established in these populations. The use of Rituxan in patients with RA who have not had prior inadequate response to one or more TNF antagonists is not recommended [See Clinical Studies (14.6)].
5.14 Retreatment in Patients with Granulomatosis with Polyangiitis (GPA) (Wegener’s Granulomatosis) and Microscopic Polyangiitis (MPA)

Limited data are available on the safety and efficacy of subsequent courses of Rituxan in patients with GPA and MPA. The safety and efficacy of retreatment with Rituxan have not been established [See Dosage and Administration (2.6), Adverse Reactions (6.3), and Clinical Studies (14.7)].

6 ADVERSE REACTIONS

The following serious adverse reactions are discussed in greater detail in other sections of the labeling:

- Infusion reactions [see Warnings and Precautions (5.1)]
- Mucocutaneous reactions [see Warnings and Precautions (5.2)]
- Hepatitis B reactivation with fulminant hepatitis [see Warnings and Precautions (5.3)]
- Progressive multifocal leukoencephalopathy [see Warnings and Precautions (5.4)]
- Tumor lysis syndrome [see Warnings and Precautions (5.5)]
- Infections [see Warnings and Precautions (5.6)]
- Cardiac arrhythmias [see Warnings and Precautions (5.7)]
- Renal toxicity [see Warnings and Precautions (5.8)]
- Bowel obstruction and perforation [see Warnings and Precautions (5.9)]

The most common adverse reactions of Rituxan (incidence ≥25%) observed in clinical trials of patients with NHL were infusion reactions, fever, lymphopenia, chills, infection, and asthenia.

The most common adverse reactions of Rituxan (incidence ≥25%) observed in clinical trials of patients with CLL were: infusion reactions and neutropenia.

6.1 Clinical Trials Experience in Lymphoid Malignancies

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

The data described below reflect exposure to Rituxan in 2783 patients, with exposures ranging from a single infusion up to 2 years. Rituxan was studied in both single-arm and controlled trials (n=356 and n=2427). The population included 1180 patients with low grade or follicular lymphoma, 927 patients with DLBCL, and 676 patients with CLL. Most NHL patients received Rituxan as an infusion of 375 mg/m² per infusion, given as a single agent weekly for up to 8 doses, in combination with chemotherapy for up to 8 doses, or following chemotherapy for up to 16 doses. CLL patients received Rituxan 375 mg/m² as an initial infusion followed by 500 mg/m² for up to 5 doses, in combination with fludarabine and cyclophosphamide. Seventy-one percent of CLL patients received 6 cycles and 90% received at least 3 cycles of Rituxan-based therapy.

Infusion Reactions

In the majority of patients with NHL, infusion reactions consisting of fever, chills/rigors, nausea, pruritus, angioedema, hypotension, headache, bronchospasm, urticaria, rash, vomiting, myalgia, dizziness, or hypertension occurred during the first Rituxan infusion. Infusion reactions typically occurred within 30 to 120 minutes of beginning the first infusion and resolved with slowing or interruption of the Rituxan infusion and with supportive care (diphenhydramine, acetaminophen, and intravenous saline). The incidence of infusion reactions was highest during the first infusion (77%) and decreased with each subsequent infusion. [See Boxed Warning, Warnings and Precautions (5.1)]. In patients with previously untreated follicular NHL or previously untreated DLBCL, who did not experience a Grade 3 or 4 infusion-related reaction in Cycle 1 and received a 90-minute infusion of Rituxan at Cycle 2, the incidence of Grade 3-4 infusion-related reactions on the day of, or day after the infusion was 1.1% (95% CI [0.3%, 2.8%]). For Cycles 2-8, the incidence of Grade 3-4 infusion reactions on the day of or day after the 90-minute infusion, was 2.8% (95% CI [1.3%, 5.0%]). [See Warnings and Precautions (5.1), Clinical Studies (14.4)].
Infections

Serious infections (NCI CTCAE Grade 3 or 4), including sepsis, occurred in less than 5% of patients with NHL in the single-arm studies. The overall incidence of infections was 31% (bacterial 19%, viral 10%, unknown 6%, and fungal 1%). [See Warnings and Precautions (5.4), (5.5), (5.6)].

In randomized, controlled studies where Rituxan was administered following chemotherapy for the treatment of follicular or low-grade NHL, the rate of infection was higher among patients who received Rituxan. In diffuse large B-cell lymphoma patients, viral infections occurred more frequently in those who received Rituxan.

Cytopenias and hypogammaglobulinemia

In patients with NHL receiving rituximab monotherapy, NCI-CTC Grade 3 and 4 cytopenias were reported in 48% of patients. These included lymphopenia (40%), neutropenia (6%), leukopenia (4%), anemia (3%), and thrombocytopenia (2%). The median duration of lymphopenia was 14 days (range, 1–588 days) and of neutropenia was 13 days (range, 2–116 days). A single occurrence of transient aplastic anemia (pure red cell aplasia) and two occurrences of hemolytic anemia following Rituxan therapy occurred during the single-arm studies.

In studies of monotherapy, Rituxan-induced B-cell depletion occurred in 70% to 80% of patients with NHL. Decreased IgM and IgG serum levels occurred in 14% of these patients.

In CLL trials, the frequency of prolonged neutropenia and late-onset neutropenia was higher in patients treated with R-FC compared to patients treated with FC. Prolonged neutropenia is defined as Grade 3-4 neutropenia that has not resolved between 24 and 42 days after the last dose of study treatment. Late-onset neutropenia is defined as Grade 3-4 neutropenia starting at least 42 days after the last treatment dose.

In patients with previously untreated CLL, the frequency of prolonged neutropenia was 8.5% for patients who received R-FC (n=402) and 5.8% for patients who received FC (n=398). In patients who did not have prolonged neutropenia, the frequency of late-onset neutropenia was 14.8% of 209 patients who received R-FC and 4.3% of 230 patients who received FC. For patients with previously treated CLL, the frequency of prolonged neutropenia was 24.8% for patients who received R-FC (n=274) and 19.1% for patients who received FC (n=274). In patients who did not have prolonged neutropenia, the frequency of late-onset neutropenia was 38.7% in 160 patients who received R-FC and 13.6% of 147 patients who received FC.

Relapsed or Refractory, Low-Grade NHL

Adverse reactions in Table 1 occurred in 356 patients with relapsed or refractory, low-grade or follicular, CD20-positive, B-cell NHL treated in single-arm studies of Rituxan administered as a single agent [See Clinical Studies (14.1)]. Most patients received Rituxan 375 mg/m² weekly for 4 doses.
Table 1
Incidence of Adverse Reactions in ≥5% of
Patients with Relapsed or Refractory, Low-Grade or Follicular
NHL, Receiving Single-agent Rituxan (N=356)\(^{a,b}\)

<table>
<thead>
<tr>
<th>Category</th>
<th>All Grades (%)</th>
<th>Grade 3 and 4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any Adverse Reactions</td>
<td>99</td>
<td>57</td>
</tr>
<tr>
<td>Body as a Whole</td>
<td>86</td>
<td>10</td>
</tr>
<tr>
<td>Fever</td>
<td>53</td>
<td>1</td>
</tr>
<tr>
<td>Chills</td>
<td>33</td>
<td>3</td>
</tr>
<tr>
<td>Infection</td>
<td>31</td>
<td>4</td>
</tr>
<tr>
<td>Asthenia</td>
<td>26</td>
<td>1</td>
</tr>
<tr>
<td>Headache</td>
<td>19</td>
<td>1</td>
</tr>
<tr>
<td>Abdominal Pain</td>
<td>14</td>
<td>1</td>
</tr>
<tr>
<td>Pain</td>
<td>12</td>
<td>1</td>
</tr>
<tr>
<td>Back Pain</td>
<td>10</td>
<td>1</td>
</tr>
<tr>
<td>Throat Irritation</td>
<td>9</td>
<td>0</td>
</tr>
<tr>
<td>Flushing</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>Heme and Lymphatic System</td>
<td>67</td>
<td>48</td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>48</td>
<td>40</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>14</td>
<td>4</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>14</td>
<td>6</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>12</td>
<td>2</td>
</tr>
<tr>
<td>Anemia</td>
<td>8</td>
<td>3</td>
</tr>
<tr>
<td>Skin and Appendages</td>
<td>44</td>
<td>2</td>
</tr>
<tr>
<td>Night Sweats</td>
<td>15</td>
<td>1</td>
</tr>
<tr>
<td>Rash</td>
<td>15</td>
<td>1</td>
</tr>
<tr>
<td>Pruritus</td>
<td>14</td>
<td>1</td>
</tr>
<tr>
<td>Urticaria</td>
<td>8</td>
<td>1</td>
</tr>
<tr>
<td>Respiratory System</td>
<td>38</td>
<td>4</td>
</tr>
<tr>
<td>Increased Cough</td>
<td>13</td>
<td>1</td>
</tr>
<tr>
<td>Rhinitis</td>
<td>12</td>
<td>1</td>
</tr>
<tr>
<td>Bronchospasm</td>
<td>8</td>
<td>1</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>7</td>
<td>1</td>
</tr>
<tr>
<td>Sinusitis</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>Metabolic and Nutritional Disorders</td>
<td>38</td>
<td>3</td>
</tr>
<tr>
<td>Angioedema</td>
<td>11</td>
<td>1</td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>9</td>
<td>1</td>
</tr>
<tr>
<td>Peripheral Edema</td>
<td>8</td>
<td>0</td>
</tr>
<tr>
<td>LDH Increase</td>
<td>7</td>
<td>0</td>
</tr>
<tr>
<td>Digestive System</td>
<td>37</td>
<td>2</td>
</tr>
<tr>
<td>Nausea</td>
<td>23</td>
<td>1</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>10</td>
<td>1</td>
</tr>
<tr>
<td>Vomiting</td>
<td>10</td>
<td>1</td>
</tr>
<tr>
<td>Nervous System</td>
<td>32</td>
<td>1</td>
</tr>
<tr>
<td>Dizziness</td>
<td>10</td>
<td>1</td>
</tr>
<tr>
<td>Anxiety</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>Musculoskeletal System</td>
<td>26</td>
<td>3</td>
</tr>
<tr>
<td>Myalgia</td>
<td>10</td>
<td>1</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>10</td>
<td>1</td>
</tr>
</tbody>
</table>
Table 1 (cont’d)
Incidence of Adverse Reactions in ≥ 5% of Patients with Relapsed or Refractory, Low-Grade or Follicular NHL, Receiving Single-agent Rituxan (N=356)\textsuperscript{a,b}

<table>
<thead>
<tr>
<th></th>
<th>All Grades (%)</th>
<th>Grade 3 and 4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular System</td>
<td>25</td>
<td>3</td>
</tr>
<tr>
<td>Hypotension</td>
<td>10</td>
<td>1</td>
</tr>
<tr>
<td>Hypertension</td>
<td>6</td>
<td>1</td>
</tr>
</tbody>
</table>

\textsuperscript{a} Adverse reactions observed up to 12 months following Rituxan.

\textsuperscript{b} Adverse reactions graded for severity by NCI-CTC criteria.

In these single-arm Rituxan studies, bronchiolitis obliterans occurred during and up to 6 months after Rituxan infusion.

Previously Untreated, Low-Grade or Follicular, NHL

In Study 4, patients in the R-CVP arm experienced a higher incidence of infusional toxicity and neutropenia compared to patients in the CVP arm. The following adverse reactions occurred more frequently (≥5%) in patients receiving R-CVP compared to CVP alone: rash (17% vs. 5%), cough (15% vs. 6%), flushing (14% vs. 3%), rigors (10% vs. 2%), pruritus (10% vs. 1%), neutropenia (8% vs. 3%), and chest tightness (7% vs. 1%). \textsuperscript{[See Clinical Studies (14.2)]}

In Study 5, detailed safety data collection was limited to serious adverse reactions, Grade ≥ 2 infections, and Grade ≥ 3 adverse reactions. In patients receiving Rituxan as single-agent maintenance therapy following Rituxan plus chemotherapy, infections were reported more frequently compared to the observation arm (37% vs. 22%). Grade 3-4 adverse reactions occurring at a higher incidence (≥2%) in the Rituxan group were infections (4% vs. 1%) and neutropenia (4% vs. <1%).

In Study 6, the following adverse reactions were reported more frequently (≥5%) in patients receiving Rituxan following CVP compared to patients who received no further therapy: fatigue (39% vs. 14%), anemia (35% vs. 20%), peripheral sensory neuropathy (30% vs. 18%), infections (19% vs. 9%), pulmonary toxicity (18% vs. 10%), hepato-biliary toxicity (17% vs. 7%), rash and/or pruritus (17% vs. 5%), arthralgia (12% vs. 3%), and weight gain (11% vs. 4%). Neutropenia was the only Grade 3 or 4 adverse reaction that occurred more frequently (≥2%) in the Rituxan arm compared with those who received no further therapy (4% vs. 1%). \textsuperscript{[See Clinical Studies (14.3)]}

DLBCL

In Studies 7 and 8, \textsuperscript{[see Clinical Studies (14.3)]}, the following adverse reactions, regardless of severity, were reported more frequently (≥5%) in patients age ≥60 years receiving R-CHOP as compared to CHOP alone: pyrexia (56% vs. 46%), lung disorder (31% vs. 24%), cardiac disorder (29% vs. 21%), and chills (13% vs. 4%). Detailed safety data collection in these studies was primarily limited to Grade 3 and 4 adverse reactions and serious adverse reactions.

In Study 8, a review of cardiac toxicity determined that supraventricular arrhythmias or tachycardia accounted for most of the difference in cardiac disorders (4.5% for R-CHOP vs. 1.0% for CHOP).

In Study 8, a review of cardiac toxicity determined that supraventricular arrhythmias or tachycardia accounted for most of the difference in cardiac disorders (4.5% for R-CHOP vs. 1.0% for CHOP).

The following Grade 3 or 4 adverse reactions occurred more frequently among patients in the R-CHOP arm compared with those in the CHOP arm: thrombocytopenia (9% vs. 7%) and lung disorder (6% vs. 3%). Other Grade 3 or 4 adverse reactions occurring more frequently among patients receiving R-CHOP were viral infection (Study 8), neutropenia (Studies 8 and 9), and anemia (Study 9).
The data below reflect exposure to Rituxan in combination with fludarabine and cyclophosphamide in 676 patients with CLL in Study 11 or Study 12 [See Clinical Studies (14.5)]. The age range was 30–83 years and 71% were men. Detailed safety data collection in Study 11 was limited to Grade 3 and 4 adverse reactions and serious adverse reactions.

Infusion-related adverse reactions were defined by any of the following adverse events occurring during or within 24 hours of the start of infusion: nausea, pyrexia, chills, hypotension, vomiting, and dyspnea.

In Study 11, the following Grade 3 and 4 adverse reactions occurred more frequently in R-FC-treated patients compared to FC-treated patients: infusion reactions (9% in R-FC arm), neutropenia (30% vs. 19%), febrile neutropenia (9% vs. 6%), leukopenia (23% vs. 12%), and pancytopenia (3% vs. 1%).

In Study 12, the following Grade 3 or 4 adverse reactions occurred more frequently in R-FC-treated patients compared to FC-treated patients: infusion reactions (7% in R-FC arm), neutropenia (49% vs. 44%), febrile neutropenia (15% vs. 12%), thrombocytopenia (11% vs. 9%), hypotension (2% vs. 0%), and hepatitis B (2% vs. <1%). Fifty-nine percent of R-FC-treated patients experienced an infusion reaction of any severity.

6.2 Clinical Trials Experience in Rheumatoid Arthritis

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The data presented below reflect the experience in 2578 RA patients treated with Rituxan in controlled and long-term studies with a total exposure of 5014 patient-years.

Among all exposed patients, adverse reactions reported in greater than 10% of patients include infusion-related reactions, upper respiratory tract infection, nasopharyngitis, urinary tract infection, and bronchitis.

In placebo-controlled studies, patients received 2 x 500 mg or 2 x 1000 mg intravenous infusions of Rituxan or placebo, in combination with methotrexate, during a 24-week period. From these studies, 938 patients treated with Rituxan (2 x 1000 mg) or placebo have been pooled (see Table 2). Adverse reactions reported in ≥ 5% of patients were hypertension, nausea, upper respiratory tract infection, arthralgia, pyrexia and pruritus (see Table 2). The rates and types of adverse reactions in patients who received Rituxan 2 x 500 mg were similar to those observed in patients who received Rituxan 2 x 1000 mg.
**Table 2**
Incidence of All Adverse Reactions** occurring in ≥2% and at least 1% greater than placebo among rheumatoid arthritis patients in clinical studies up to week 24 (pooled)

<table>
<thead>
<tr>
<th>Preferred Term</th>
<th>Placebo + MTX</th>
<th>Rituxan + MTX</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=398</td>
<td>N=540</td>
</tr>
<tr>
<td></td>
<td>n (%)</td>
<td>n (%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>21 (5)</td>
<td>43 (8)</td>
</tr>
<tr>
<td>Nausea</td>
<td>19 (5)</td>
<td>41 (8)</td>
</tr>
<tr>
<td>Upper Respiratory Tract Infection</td>
<td>23 (6)</td>
<td>37 (7)</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>14 (4)</td>
<td>31 (6)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>8 (2)</td>
<td>27 (5)</td>
</tr>
<tr>
<td>Pruritus</td>
<td>5 (1)</td>
<td>26 (5)</td>
</tr>
<tr>
<td>Chills</td>
<td>9 (2)</td>
<td>16 (3)</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>3 (&lt;1)</td>
<td>16 (3)</td>
</tr>
<tr>
<td>Rhinitis</td>
<td>6 (2)</td>
<td>14 (3)</td>
</tr>
<tr>
<td>Paresthesia</td>
<td>3 (&lt;1)</td>
<td>12 (2)</td>
</tr>
<tr>
<td>Urticaria</td>
<td>3 (&lt;1)</td>
<td>12 (2)</td>
</tr>
<tr>
<td>Abdominal Pain Upper</td>
<td>4 (1)</td>
<td>11 (2)</td>
</tr>
<tr>
<td>Throat Irritation</td>
<td>0 (0)</td>
<td>11 (2)</td>
</tr>
<tr>
<td>Anxiety</td>
<td>5 (1)</td>
<td>9 (2)</td>
</tr>
<tr>
<td>Migraine</td>
<td>2 (&lt;1)</td>
<td>9 (2)</td>
</tr>
<tr>
<td>Asthenia</td>
<td>1 (&lt;1)</td>
<td>9 (2)</td>
</tr>
</tbody>
</table>

*These data are based on 938 patients treated in Phase 2 and 3 studies of Rituxan (2 × 1000 mg) or placebo administered in combination with methotrexate.

**Coded using MedDRA.

**Infusion Reactions**

In the Rituxan RA pooled placebo-controlled studies, 32% of Rituxan-treated patients experienced an adverse reaction during or within 24 hours following their first infusion, compared to 23% of placebo-treated patients receiving their first infusion. The incidence of adverse reactions during the 24-hour period following the second infusion, Rituxan or placebo, decreased to 11% and 13%, respectively. Acute infusion reactions (manifested by fever, chills, rigors, pruritus, urticaria/rash, angioedema, sneezing, throat irritation, cough, and/or bronchospasm, with or without associated hypotension or hypertension) were experienced by 27% of Rituxan-treated patients following their first infusion, compared to 19% of placebo-treated patients receiving their first placebo infusion. The incidence of these acute infusion reactions following the second infusion of Rituxan or placebo decreased to 9% and 11%, respectively. Serious acute infusion reactions were experienced by <1% of patients in either treatment group. Acute infusion reactions required dose modification (stopping, slowing, or interruption of the infusion) in 10% and 2% of patients receiving rituximab or placebo, respectively, after the first course. The proportion of patients experiencing acute infusion reactions decreased with subsequent courses of Rituxan. The administration of intravenous glucocorticoids prior to Rituxan infusions reduced the incidence and severity of such reactions, however, there was no clear benefit from the administration of oral glucocorticoids for the prevention of acute infusion...
reactions. Patients in clinical studies also received antihistamines and acetaminophen prior to Rituxan infusions.

**Infections**

In the pooled, placebo-controlled studies, 39% of patients in the Rituxan group experienced an infection of any type compared to 34% of patients in the placebo group. The most common infections were nasopharyngitis, upper respiratory tract infections, urinary tract infections, bronchitis, and sinusitis.

The incidence of serious infections was 2% in the Rituxan-treated patients and 1% in the placebo group.

In the experience with Rituxan in 2578 RA patients, the rate of serious infections was 4.31 per 100 patient years. The most common serious infections (≥0.5%) were pneumonia or lower respiratory tract infections, cellulitis and urinary tract infections. Fatal serious infections included pneumonia, sepsis and colitis. Rates of serious infection remained stable in patients receiving subsequent courses. In 185 Rituxan-treated RA patients with active disease, subsequent treatment with a biologic DMARD, the majority of which were TNF antagonists, did not appear to increase the rate of serious infection. Thirteen serious infections were observed in 186.1 patient years (6.99 per 100 patient years) prior to exposure and 10 were observed in 182.3 patient years (5.49 per 100 patient years) after exposure.

**Cardiac Adverse Reactions**

In the pooled, placebo-controlled studies, the proportion of patients with serious cardiovascular reactions was 1.7% and 1.3% in the Rituxan and placebo treatment groups, respectively. Three cardiovascular deaths occurred during the double-blind period of the RA studies including all rituximab regimens (3/769=0.4%) as compared to none in the placebo treatment group (0/389).

In the experience with Rituxan in 2578 RA patients, the rate of serious cardiac reactions was 1.93 per 100 patient years. The rate of myocardial infarction (MI) was 0.56 per 100 patient years (28 events in 26 patients), which is consistent with MI rates in the general RA population. These rates did not increase over three courses of Rituxan.

Since patients with RA are at increased risk for cardiovascular events compared with the general population, patients with RA should be monitored throughout the infusion and Rituxan should be discontinued in the event of a serious or life-threatening cardiac event.

**Hypophosphatemia and hyperuricemia**

In the pooled, placebo-controlled studies, newly-occurring hypophosphatemia (<2.0 mg/dl) was observed in 12% (67/540) of patients on Rituxan versus 10% (39/398) of patients on placebo. Hypophosphatemia was more common in patients who received corticosteroids. Newly-occurring hyperuricemia (>10 mg/dl) was observed in 1.5% (8/540) of patients on Rituxan versus 0.3% (1/398) of patients on placebo.

In the experience with Rituxan in RA patients, newly-occurring hypophosphatemia was observed in 21% (528/2570) of patients and newly-occurring hyperuricemia was observed in 2% (56/2570) of patients. The majority of the observed hypophosphatemia occurred at the time of the infusions and was transient.

**Retreatment in Patients with RA**

In the experience with Rituxan in RA patients, 2578 patients have been exposed to Rituxan and have received up to 10 courses of Rituxan in RA clinical trials, with 1890, 1043, and 425 patients having received at least two, three, and four courses, respectively. Most of the patients who received additional courses did so 24 weeks or more after the previous course and none were retreated sooner than 16 weeks. The rates and types of adverse reactions reported for subsequent courses of Rituxan were similar to rates and types seen for a single course of Rituxan.
In RA Study 2, where all patients initially received Rituxan, the safety profile of patients who were retreated with Rituxan was similar to those who were retreated with placebo [See Clinical Studies (14.6), and Dosage and Administration (2.5)].

6.3 Clinical Trials Experience in Granulomatosis with Polyangiitis (GPA) (Wegener’s Granulomatosis) and Microscopic Polyangiitis (MPA)

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The data presented below reflect the experience in 197 patients with GPA and MPA treated with Rituxan or cyclophosphamide in a single controlled study, which was conducted in two phases: a 6 month randomized, double-blind, double-dummy, active-controlled remission induction phase and an additional 12 month remission maintenance phase. In the 6-month remission induction phase, 197 patients with GPA and MPA were randomized to either Rituxan 375 mg/ m² once weekly for 4 weeks plus glucocorticoids, or oral cyclophosphamide 2 mg/kg daily (adjusted for renal function, white blood cell count, and other factors) plus glucocorticoids to induce remission. Once remission was achieved or at the end of the 6 month remission induction period, the cyclophosphamide group received azathioprine to maintain remission. The Rituxan group did not receive additional therapy to maintain remission. The primary analysis was at the end of the 6 month remission induction period and the safety results for this period are described below.

Adverse reactions presented below in Table 3 were adverse events which occurred at a rate of greater than or equal to 10% in the Rituxan group. This table reflects experience in 99 GPA and MPA patients treated with Rituxan, with a total of 47.6 patient-years of observation and 98 GPA and MPA patients treated with cyclophosphamide, with a total of 47.0 patient-years of observation. Infection was the most common category of adverse events reported (47-62%) and is discussed below.
Table 3
Incidence of All Adverse Reactions Occurring in ≥ 10% of Rituxan-treated GPA and MPA Patients in the Clinical Study Up to Month 6

<table>
<thead>
<tr>
<th>Preferred Term</th>
<th>Rituxan N=99 n (%)</th>
<th>Cyclophosphamide N=98 n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>18 (18%)</td>
<td>20 (20%)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>17 (17%)</td>
<td>12 (12%)</td>
</tr>
<tr>
<td>Headache</td>
<td>17 (17%)</td>
<td>19 (19%)</td>
</tr>
<tr>
<td>Muscle spasms</td>
<td>17 (17%)</td>
<td>15 (15%)</td>
</tr>
<tr>
<td>Anemia</td>
<td>16 (16%)</td>
<td>20 (20%)</td>
</tr>
<tr>
<td>Peripheral edema</td>
<td>16 (16%)</td>
<td>6 (6%)</td>
</tr>
<tr>
<td>Insomnia</td>
<td>14 (14%)</td>
<td>12 (12%)</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>13 (13%)</td>
<td>9 (9%)</td>
</tr>
<tr>
<td>Cough</td>
<td>13 (13%)</td>
<td>11 (11%)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>13 (13%)</td>
<td>21 (21%)</td>
</tr>
<tr>
<td>Increased ALT</td>
<td>13 (13%)</td>
<td>15 (15%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>12 (12%)</td>
<td>5 (5%)</td>
</tr>
<tr>
<td>Epistaxis</td>
<td>11 (11%)</td>
<td>6 (6%)</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>10 (10%)</td>
<td>11 (11%)</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>10 (10%)</td>
<td>26 (27%)</td>
</tr>
<tr>
<td>Rash</td>
<td>10 (10%)</td>
<td>17 (17%)</td>
</tr>
</tbody>
</table>

*The study design allowed for crossover or treatment by best medical judgment, and 13 patients in each treatment group received a second therapy during the 6 month study period.

Infusion Reactions

Infusion-related reactions in the active-controlled, double-blind study were defined as any adverse event occurring within 24 hours of an infusion and considered to be infusion-related by investigators. Among the 99 patients treated with Rituxan, 12% experienced at least one infusion related reaction, compared with 11% of the 98 patients in the cyclophosphamide group. Infusion-related reactions included cytokine release syndrome, flushing, throat irritation, and tremor. In the Rituxan group, the proportion of patients experiencing an infusion related reaction was 12%, 5%, 4%, and 1% following the first, second, third, and fourth infusions, respectively. Patients were pre-medicated with antihistamine and acetaminophen before each Rituxan infusion and were on background oral corticosteroids which may have mitigated or masked an infusion reaction; however, there is insufficient evidence to determine whether premedication diminishes the frequency or severity of infusion reactions.

Infections

In the active-controlled, double-blind study, 62% (61/99) of patients in the Rituxan group experienced an infection of any type compared to 47% (46/98) patients in the cyclophosphamide group by Month 6. The most common infections in the Rituxan group were upper respiratory tract infections, urinary tract infections, and herpes zoster.
The incidence of serious infections was 11% in the Rituxan-treated patients and 10% in the cyclophosphamide treated patients, with rates of approximately 25 and 28 per 100 patient-years, respectively. The most common serious infection was pneumonia.

**Hypogammaglobulinemia**

Hypogammaglobulinemia (IgA, IgG or IgM below the lower limit of normal) has been observed in patients with GPA and MPA treated with Rituxan. At 6 months, in the Rituxan group, 27%, 58% and 51% of patients with normal immunoglobulin levels at baseline, had low IgA, IgG and IgM levels, respectively compared to 25%, 50% and 46% in the cyclophosphamide group.

**Retreatment in Patients with GPA and MPA**

In the active-controlled, double-blind study, subsequent courses of Rituxan were allowed for patients experiencing a relapse of disease. The limited data preclude any conclusions regarding the safety of subsequent courses of Rituxan with GPA and MPA [See Dosage and Administration (2.6), and Warnings and Precautions (5.14)].

**6.4 Immunogenicity**

As with all therapeutic proteins, there is a potential for immunogenicity. The observed incidence of antibody (including neutralizing antibody) positivity in an assay is highly dependent on several factors including assay sensitivity and specificity, assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to Rituxan with the incidence of antibodies to other products may be misleading.

Using an ELISA assay, anti-human anti-chimeric antibody (HACA) was detected in 4 of 356 (1.1%) patients with low-grade or follicular NHL receiving single-agent Rituxan. Three of the four patients had an objective clinical response.

A total of 273/2578 (11%) patients with RA tested positive for HACA at any time after receiving Rituxan. HACA positivity was not associated with increased infusion reactions or other adverse reactions. Upon further treatment, the proportions of patients with infusion reactions were similar between HACA positive and negative patients, and most reactions were mild to moderate. Four HACA positive patients had serious infusion reactions, and the temporal relationship between HACA positivity and infusion reaction was variable.

A total of 23/99 (23%) Rituxan-treated patients with GPA and MPA tested positive for HACA by 18 months. The clinical relevance of HACA formation in Rituxan-treated patients is unclear.

**6.5 Postmarketing Experience**

Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. Decisions to include these reactions in labeling are typically based on one or more of the following factors: (1) seriousness of the reaction, (2) frequency of reporting, or (3) strength of causal connection to Rituxan.

- Hematologic: prolonged pancytopenia, marrow hypoplasia, Grade 3-4 prolonged or late-onset neutropenia, hyperviscosity syndrome in Waldenstrom’s macroglobulinemia, prolonged hypogammaglobulinemia [See Warnings and Precautions (5.6)].
- Cardiac: fatal cardiac failure.
- Immune/Autoimmune Events: uveitis, optic neuritis, systemic vasculitis, pleuritis, lupus-like syndrome, serum sickness, polyarticular arthritis, and vasculitis with rash.
- Infection: viral infections, including progressive multifocal leukoencephalopathy (PML), increase in fatal infections in HIV-associated lymphoma, and a reported increased incidence of Grade 3 and 4 infections [See Warnings and Precautions (5.6)].
- Neoplasia: disease progression of Kaposi’s sarcoma.
- Skin: severe mucocutaneous reactions.
- Gastrointestinal: bowel obstruction and perforation.
- Pulmonary: fatal bronchiolitis obliterans and fatal interstitial lung disease.

7 DRUG INTERACTIONS

Formal drug interaction studies have not been performed with Rituxan. In patients with CLL, Rituxan did not alter systemic exposure to fludarabine or cyclophosphamide. In clinical trials of patients with RA, concomitant administration of methotrexate or cyclophosphamide did not alter the pharmacokinetics of rituximab.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

Risk Summary

There are no adequate and well-controlled studies of rituximab in pregnant women. Women of childbearing potential should use effective contraception while receiving Rituxan and for 12 months following treatment. Rituxan should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Human data

Postmarketing data indicate that B-cell lymphocytopenia generally lasting less than six months can occur in infants exposed to rituximab in-utero. Rituximab was detected postnatally in the serum of infants exposed in-utero.

Animal Data

An embryo-fetal developmental toxicity study was performed on pregnant cynomolgus monkeys. Pregnant animals received rituximab via the intravenous route during early gestation (organogenesis period; post-coitum days 20 through 50). Rituximab was administered as loading doses on postcoitum (PC) Days 20, 21 and 22, at 15, 37.5 or 75 mg/kg/day, and then weekly on PC Days 29, 36, 43 and 50, at 20, 50 or 100 mg/kg/week. The 100 mg/kg/week dose resulted in 80% of the exposure (based on AUC) of those achieved following a dose of 2 grams in humans. Rituximab crosses the monkey placenta. Exposed offspring did not exhibit any teratogenic effects but did have decreased lymphoid tissue B cells.

A subsequent pre-and postnatal reproductive toxicity study in cynomolgus monkeys was completed to assess developmental effects including the recovery of B cells and immune function in infants exposed to rituximab in utero. Animals were treated with a loading dose of 0, 15, or 75 mg/kg every day for 3 days, followed by weekly dosing with 0, 20, or 100 mg/kg dose. Subsets of pregnant females were treated from PC Day 20 through postpartum Day 78, PC Day 76 through PC Day 134, and from PC Day 132 through delivery and postpartum Day 28. Regardless of the timing of treatment, decreased B cells and immunosuppression were noted in the offspring of rituximab-treated pregnant animals. The B-cell counts returned to normal levels, and immunologic function was restored within 6 months postpartum.

8.3 Nursing Mothers

It is not known whether Rituxan is secreted into human milk. However, Rituxan is secreted in the milk of lactating cynomolgus monkeys, and IgG is excreted in human milk. Published data suggest that antibodies in breast milk do not enter the neonatal and infant circulations in substantial amounts. The unknown risks to the infant from oral ingestion of Rituxan should be weighed against the known benefits of breastfeeding.

8.4 Pediatric Use

FDA has not required pediatric studies in polyarticular juvenile idiopathic arthritis (PJIA) patients ages 0 to 16 due to concerns regarding the potential for prolonged immunosuppression as a result of B-cell depletion in the developing juvenile immune system. Hypogammaglobulinemia has been observed in pediatric patients treated with Rituxan. The safety and effectiveness of Rituxan in pediatric patients have not been established.
8.5 Geriatric Use

Diffuse Large B-Cell NHL

Among patients with DLBCL evaluated in three randomized, active-controlled trials, 927 patients received Rituxan in combination with chemotherapy. Of these, 396 (43%) were age 65 or greater and 123 (13%) were age 75 or greater. No overall differences in effectiveness were observed between these patients and younger patients. Cardiac adverse reactions, mostly supraventricular arrhythmias, occurred more frequently among elderly patients. Serious pulmonary adverse reactions were also more common among the elderly, including pneumonia and pneumonitis.

Low-Grade or Follicular Non-Hodgkin’s Lymphoma

Patients with previously untreated follicular NHL evaluated in Study 5 were randomized to Rituxan as single-agent maintenance therapy (n=505) or observation (n=513) after achieving a response to Rituxan in combination with chemotherapy. Of these, 123 (24%) patients in the Rituxan arm were age 65 or older. No overall differences in safety or effectiveness were observed between these patients and younger patients. Other clinical studies of Rituxan in low-grade or follicular, CD20-positive, B-cell NHL did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger subjects.

Chronic Lymphocytic Leukemia

Among patients with CLL evaluated in two randomized active-controlled trials, 243 of 676 Rituxan-treated patients (36%) were 65 years of age or older; of these, 100 Rituxan-treated patients (15%) were 70 years of age or older.

In exploratory analyses defined by age, there was no observed benefit from the addition of Rituxan to fludarabine and cyclophosphamide among patients 70 years of age or older in Study 11 or in Study 12; there was also no observed benefit from the addition of Rituxan to fludarabine and cyclophosphamide among patients 65 years of age or older in Study 12. Patients 70 years or older received lower dose intensity of fludarabine and cyclophosphamide compared to younger patients, regardless of the addition of Rituxan. In Study 11, the dose intensity of Rituxan was similar in older and younger patients, however in Study 12 older patients received a lower dose intensity of Rituxan.

The incidence of Grade 3 and 4 adverse reactions was higher among patients receiving R-FC who were 70 years or older compared to younger patients for neutropenia [44% vs. 31% (Study 11); 56% vs. 39% (Study 12)], febrile neutropenia [16% vs. 6% (Study 10)], anemia [5% vs. 2% (Study 11); 21% vs. 10% (Study 12)], thrombocytopenia [19% vs. 8% (Study 12)], pancytopenia [7% vs. 2% (Study 11); 7% vs. 2% (Study 12)] and infections [30% vs. 14% (Study 12)].

Rheumatoid Arthritis

Among the 2578 patients in global RA studies completed to date, 12% were 65–75 years old and 2% were 75 years old and older. The incidences of adverse reactions were similar between older and younger patients. The rates of serious adverse reactions, including serious infections, malignancies, and cardiovascular events were higher in older patients.

Granulomatosis with Polyangiitis (GPA) (Wegener’s Granulomatosis) and Microscopic Polyangiitis

Of the 99 Rituxan-treated GPA and MPA patients, 36 (36%) were 65 years old and over, while 8 (8%) were 75 years and over. No overall differences in efficacy were observed between patients that were 65 years old and over and younger patients. The overall incidence and rate of all serious adverse events was higher in patients 65 years old and over. The clinical study did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger subjects.

10 OVERDOSAGE

There has been no experience of overdosage with Rituxan.
11 DESCRIPTION

Rituxan® (rituximab) is a genetically engineered chimeric murine/human monoclonal IgG1 kappa antibody directed against the CD20 antigen. Rituximab has an approximate molecular weight of 145 kD. Rituximab has a binding affinity for the CD20 antigen of approximately 8.0 nM.

Rituximab is produced by mammalian cell (Chinese Hamster Ovary) suspension culture in a nutrient medium containing the antibiotic gentamicin. Gentamicin is not detectable in the final product. Rituxan is a sterile, clear, colorless, preservative-free liquid concentrate for intravenous administration. Rituxan is supplied at a concentration of 10 mg/mL in either 100 mg/10 mL or 500 mg/50 mL single-use vials. The product is formulated in polysorbate 80 (0.7 mg/mL), sodium chloride (9 mg/mL), sodium citrate dihydrate (7.35 mg/mL), and Water for Injection. The pH is 6.5.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Rituximab is a monoclonal antibody that targets the CD20 antigen expressed on the surface of pre-B and mature B-lymphocytes. Upon binding to CD20, rituximab mediates B-cell lysis. Possible mechanisms of cell lysis include complement dependent cytotoxicity (CDC) and antibody dependent cell mediated cytotoxicity (ADCC). The antibody induced apoptosis in the DHL 4 human B cell lymphoma cell line.

B cells are believed to play a role in the pathogenesis of rheumatoid arthritis (RA) and associated chronic synovitis. In this setting, B cells may be acting at multiple sites in the autoimmune/inflammatory process, including through production of rheumatoid factor (RF) and other autoantibodies, antigen presentation, T-cell activation, and/or proinflammatory cytokine production.

12.2 Pharmacodynamics

Non-Hodgkin’s Lymphoma (NHL)

In NHL patients, administration of Rituxan resulted in depletion of circulating and tissue-based B cells. Among 166 patients in Study 1, circulating CD19-positive B cells were depleted within the first three weeks with sustained depletion for up to 6 to 9 months post treatment in 83% of patients. B-cell recovery began at approximately 6 months and median B-cell levels returned to normal by 12 months following completion of treatment.

There were sustained and statistically significant reductions in both IgM and IgG serum levels observed from 5 through 11 months following rituximab administration; 14% of patients had IgM and/or IgG serum levels below the normal range.

Rheumatoid Arthritis

In RA patients, treatment with Rituxan induced depletion of peripheral B lymphocytes, with the majority of patients demonstrating near complete depletion (CD19 counts below the lower limit of quantification, 20 cells/µl) within 2 weeks after receiving the first dose of Rituxan. The majority of patients showed peripheral B-cell depletion for at least 6 months. A small proportion of patients (~4%) had prolonged peripheral B-cell depletion lasting more than 3 years after a single course of treatment.

Total serum immunoglobulin levels, IgM, IgG, and IgA were reduced at 6 months with the greatest change observed in IgM. At Week 24 of the first course of Rituxan treatment, small proportions of patients experienced decreases in IgM (10%), IgG (2.8%), and IgA (0.8%) levels below the lower limit of normal (LLN). In the experience with Rituxan in RA patients during repeated Rituxan treatment, 23.3%, 5.5%, and 0.5% of patients experienced decreases in IgM, IgG, and IgA concentrations below LLN at any time after receiving Rituxan, respectively. The clinical consequences of decreases in immunoglobulin levels in RA patients treated with Rituxan are unclear.

Treatment with rituximab in patients with RA was associated with reduction of certain biologic markers of inflammation such as interleukin-6 (IL-6), C-reactive protein (CRP), serum amyloid
protein (SAA), S100 A8/S100 A9 heterodimer complex (S100 A8/9), anti-citrullinated peptide (anti-CCP), and RF.

**Granulomatosis with Polyangiitis (GPA) (Wegener’s Granulomatosis) and Microscopic Polyangiitis**

In GPA and MPA patients, peripheral blood CD19 B-cells depleted to less than 10 cells/μl following the first two infusions of Rituxan, and remained at that level in most (84%) patients through Month 6. By Month 12, the majority of patients (81%) showed signs of B-cell return with counts >10 cells/μL. By Month 18, most patients (87%) had counts >10 cells/μL.

### 12.3 Pharmacokinetics

**Non-Hodgkin’s Lymphoma (NHL)**

Pharmacokinetics were characterized in 203 NHL patients receiving 375 mg/m² Rituxan weekly by intravenous infusion for 4 doses. Rituximab was detectable in the serum of patients 3 to 6 months after completion of treatment.

The pharmacokinetic profile of rituximab when administered as 6 infusions of 375 mg/m² in combination with 6 cycles of CHOP chemotherapy was similar to that seen with rituximab alone.

Based on a population pharmacokinetic analysis of data from 298 NHL patients who received rituximab once weekly or once every three weeks, the estimated median terminal elimination half-life was 22 days (range, 6.1 to 52 days). Patients with higher CD19-positive cell counts or larger measurable tumor lesions at pretreatment had a higher clearance. However, dose adjustment for pretreatment CD19 count or size of tumor lesion is not necessary. Age and gender had no effect on the pharmacokinetics of rituximab.

Pharmacokinetics were characterized in 21 patients with CLL receiving rituximab according to the recommended dose and schedule. The estimated median terminal half-life of rituximab was 32 days (range, 14 to 62 days).

**Rheumatoid Arthritis**

Following administration of 2 doses of Rituxan in patients with RA, the mean (± S.D.; % CV) concentrations after the first infusion (Cmax first) and second infusion (Cmax second) were 157 (± 46; 29%) and 183 (± 55; 30%) mcg/mL, and 318 (± 86; 27%) and 381 (± 98; 26%) mcg/mL for the 2 × 500 mg and 2 × 1000 mg doses, respectively.

Based on a population pharmacokinetic analysis of data from 2005 RA patients who received Rituxan, the estimated clearance of rituximab was 0.335 L/day; volume of distribution was 3.1 L and mean terminal elimination half-life was 18.0 days (range, 5.17 to 77.5 days). Age, weight and gender had no effect on the pharmacokinetics of rituximab in RA patients.

**Granulomatosis with Polyangiitis (GPA) (Wegener’s Granulomatosis) and Microscopic Polyangiitis**

Based on the population pharmacokinetic analysis of data in 97 GPA and MPA patients who received 375 mg/m² rituximab once weekly by intravenous infusion for four weeks, the estimated median terminal elimination half-life was 23 days (range, 9 to 49 days). Rituximab mean clearance and volume of distribution were 0.312 L/day (range, 0.115 to 0.728 L/day) and 4.50 L (range, 2.21 to 7.52 L) respectively. Male patients and patients with higher BSA or positive HACA levels have higher clearance. However, further dose adjustment based on gender or HACA status is not necessary.

The pharmacokinetics of rituximab have not been studied in children and adolescents. No formal studies were conducted to examine the effects of either renal or hepatic impairment on the pharmacokinetics of rituximab.

### 13 NONCLINICAL TOXICOLOGY

**13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

No long-term animal studies have been performed to establish the carcinogenic or mutagenic potential of Rituxan or to determine potential effects on fertility in males or females.
14 CLINICAL STUDIES

14.1 Relapsed or Refractory, Low-Grade or Follicular, CD20-Positive, B-Cell NHL

The safety and effectiveness of Rituxan in relapsed, refractory CD20+ NHL were demonstrated in 3 single-arm studies enrolling 296 patients.

Study 1

A multicenter, open-label, single-arm study was conducted in 166 patients with relapsed or refractory, low-grade or follicular, B-cell NHL who received 375 mg/m² of Rituxan given as an intravenous infusion weekly for 4 doses. Patients with tumor masses > 10 cm or with > 5000 lymphocytes/µL in the peripheral blood were excluded from the study.

Results are summarized in Table 4. The median time to onset of response was 50 days. Disease-related signs and symptoms (including B-symptoms) resolved in 64% (25/39) of those patients with such symptoms at study entry.

Study 2

In a multicenter, single-arm study, 37 patients with relapsed or refractory, low-grade NHL received 375 mg/m² of Rituxan weekly for 8 doses. Results are summarized in Table 4.

Study 3

In a multicenter, single-arm study, 60 patients received 375 mg/m² of Rituxan weekly for 4 doses. All patients had relapsed or refractory, low-grade or follicular, B-cell NHL and had achieved an objective clinical response to Rituxan administered 3.8–35.6 months (median 14.5 months) prior to retreatment with Rituxan. Of these 60 patients, 5 received more than one additional course of Rituxan. Results are summarized in Table 4.

Bulky Disease

In pooled data from studies 1 and 3, 39 patients with bulky (single lesion > 10 cm in diameter) and relapsed or refractory, low-grade NHL received Rituxan 375 mg/m² weekly for 4 doses. Results are summarized in Table 4.

Table 4

<table>
<thead>
<tr>
<th>Study</th>
<th>Schedule</th>
<th>Overall Response Rate</th>
<th>Complete Response Rate</th>
<th>Median Duration of Response</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(Months) [Range]</td>
</tr>
<tr>
<td>Study 1</td>
<td>Weekly × 4</td>
<td>N=166</td>
<td>48%</td>
<td>6%</td>
</tr>
<tr>
<td>Study 2</td>
<td>Weekly × 8</td>
<td>N=37</td>
<td>57%</td>
<td>14%</td>
</tr>
<tr>
<td>Study 1 and Study 3</td>
<td>Bulky disease, Weekly × 4</td>
<td>N=39</td>
<td>36%</td>
<td>3%</td>
</tr>
<tr>
<td>Study 3</td>
<td>Retreatment, Weekly × 4</td>
<td>N=60</td>
<td>38%</td>
<td>10%</td>
</tr>
</tbody>
</table>

a Six of these patients are included in the first column. Thus, data from 296 intent-to-treat patients are provided in this table.
b Kaplan-Meier projected with observed range.
c “+” indicates an ongoing response.
d Duration of response: interval from the onset of response to disease progression.

14.2 Previously Untreated, Low-Grade or Follicular, CD20-Positive, B-Cell NHL

The safety and effectiveness of Rituxan in previously untreated, low-grade or follicular, CD20+ NHL were demonstrated in 3 randomized, controlled trials enrolling 1,662 patients.
**Study 4**

A total of 322 patients with previously untreated follicular NHL were randomized (1:1) to receive up to eight 3-week cycles of CVP chemotherapy alone (CVP) or in combination with Rituxan 375 mg/m² on Day 1 of each cycle (R-CVP) in an open-label, multicenter study. The main outcome measure of the study was progression-free survival (PFS) defined as the time from randomization to the first of progression, relapse, or death.

Twenty-six percent of the study population was >60 years of age, 99% had Stage III or IV disease, and 50% had an International Prognostic Index (IPI) score ≥2. The results for PFS as determined by a blinded, independent assessment of progression are presented in Table 5. The point estimates may be influenced by the presence of informative censoring. The PFS results based on investigator assessment of progression were similar to those obtained by the independent review assessment.

**Table 5**

**Efficacy Results in Study 4**

<table>
<thead>
<tr>
<th>Study Arm</th>
<th>R-CVP (N=162)</th>
<th>CVP (N=160)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median PFS (years)</td>
<td>2.4</td>
<td>1.4</td>
</tr>
<tr>
<td>Hazard ratio (95% CI)</td>
<td>0.44 (0.29, 0.65)</td>
<td></td>
</tr>
</tbody>
</table>

*a p < 0.0001, two-sided stratified log-rank test.  
b Estimates of Cox regression stratified by center.

**Study 5**

An open-label, multicenter, randomized (1:1) study was conducted in 1,018 patients with previously untreated follicular NHL who achieved a response (CR or PR) to Rituxan in combination with chemotherapy. Patients were randomized to Rituxan as single-agent maintenance therapy, 375 mg/m² every 8 weeks for up to 12 doses or to observation. Rituxan was initiated at 8 weeks following completion of chemotherapy. The main outcome measure of the study was progression-free survival (PFS), defined as the time from randomization in the maintenance/observation phase to progression, relapse, or death, as determined by independent review.

Of the randomized patients, 40% were ≥60 years of age, 70% had Stage IV disease, 96% had ECOG performance status (PS) 0–1, and 42% had FLIPI scores of 3–5. Prior to randomization to maintenance therapy, patients had received R-CHOP (75%), R-CVP (22%), or R-FCM (3%); 71% had a complete or unconfirmed complete response and 28% had a partial response.

PFS was longer in patients randomized to Rituxan as single agent maintenance therapy (HR: 0.54, 95% CI: 0.42, 0.70). The PFS results based on investigator assessment of progression were similar to those obtained by the independent review assessment.
A total of 322 patients with previously untreated low-grade, B-cell NHL who did not progress after 6 or 8 cycles of CVP chemotherapy were enrolled in an open-label, multicenter, randomized trial. Patients were randomized (1:1) to receive Rituxan, 375 mg/m² intravenous infusion, once weekly for 4 doses every 6 months for up to 16 doses or no further therapeutic intervention. The main outcome measure of the study was progression-free survival defined as the time from randomization to progression, relapse, or death. Thirty-seven percent of the study population was >60 years of age, 99% had Stage III or IV disease, and 63% had an IPI score ≥2.

There was a reduction in the risk of progression, relapse, or death (hazard ratio estimate in the range of 0.36 to 0.49) for patients randomized to Rituxan as compared to those who received no additional treatment.

14.3 Diffuse Large B-Cell NHL (DLBCL)

The safety and effectiveness of Rituxan were evaluated in three randomized, active-controlled, open-label, multicenter studies with a collective enrollment of 1854 patients. Patients with previously untreated diffuse large B-cell NHL received Rituxan in combination with cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) or other anthracycline-based chemotherapy regimens.

Study 7

A total of 632 patients age ≥ 60 years with DLBCL (including primary mediastinal B-cell lymphoma) were randomized in a 1:1 ratio to treatment with CHOP or R-CHOP. Patients received 6 or 8 cycles of CHOP, each cycle lasting 21 days. All patients in the R-CHOP arm received 4 doses of Rituxan 375 mg/m² on Days −7 and −3 (prior to Cycle 1) and 48–72 hours prior to Cycles 3 and 5. Patients who received 8 cycles of CHOP also received Rituxan prior to Cycle 7. The main outcome measure of the study was progression-free survival, defined as the time from randomization to the first of progression, relapse, or death. Responding patients underwent a second randomization to receive Rituxan or no further therapy.

Among all enrolled patients, 62% had centrally confirmed DLBCL histology, 73% had Stage III–IV disease, 56% had IPI scores ≥ 2, 86% had ECOG performance status of < 2, 57% had
elevated LDH levels, and 30% had two or more extranodal disease sites involved. Efficacy results are presented in Table 6. These results reflect a statistical approach which allows for an evaluation of Rituxan administered in the induction setting that excludes any potential impact of Rituxan given after the second randomization.

Analysis of results after the second randomization in Study 7 demonstrates that for patients randomized to R-CHOP, additional Rituxan exposure beyond induction was not associated with further improvements in progression-free survival or overall survival.

**Study 8**

A total of 399 patients with DLBCL, age ≥ 60 years, were randomized in a 1:1 ratio to receive CHOP or R-CHOP. All patients received up to eight 3-week cycles of CHOP induction; patients in the R-CHOP arm received Rituxan 375 mg/m² on Day 1 of each cycle. The main outcome measure of the study was event-free survival, defined as the time from randomization to relapse, progression, change in therapy, or death from any cause. Among all enrolled patients, 80% had Stage III or IV disease, 60% of patients had an age-adjusted IPI ≥ 2, 80% had ECOG performance status scores < 2, 66% had elevated LDH levels, and 52% had extranodal involvement in at least two sites. Efficacy results are presented in Table 6.

**Study 9**

A total of 823 patients with DLBCL, aged 18–60 years, were randomized in a 1:1 ratio to receive an anthracycline-containing chemotherapy regimen alone or in combination with Rituxan. The main outcome measure of the study was time to treatment failure, defined as time from randomization to the earliest of progressive disease, failure to achieve a complete response, relapse, or death. Among all enrolled patients, 28% had Stage III–IV disease, 100% had IPI scores of ≤ 1, 99% had ECOG performance status of < 2, 29% had elevated LDH levels, 49% had bulky disease, and 34% had extranodal involvement. Efficacy results are presented in Table 6.

### Table 6

<table>
<thead>
<tr>
<th></th>
<th>Study 7 (n=632)</th>
<th>Study 8 (n=399)</th>
<th>Study 9 (n=823)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>R-CHOP CHOP</td>
<td>R-CHOP CHOP</td>
<td>R-Chemo Chemo</td>
</tr>
<tr>
<td>Main outcome</td>
<td></td>
<td></td>
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<tr>
<td>Progression-free survival (years)</td>
<td>3.1 1.6</td>
<td>2.9 1.1</td>
<td>NE  NE</td>
</tr>
<tr>
<td>Event-free survival (years)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Time to treatment failure (years)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Median of main outcome measure</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hazard ratio&lt;sup&gt;d&lt;/sup&gt;</td>
<td>0.69&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.60&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.45&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Overall survival at 2 years&lt;sup&gt;c&lt;/sup&gt;</td>
<td>74% 63%</td>
<td>69% 58%</td>
<td>95% 86%</td>
</tr>
<tr>
<td>Hazard ratio&lt;sup&gt;d&lt;/sup&gt;</td>
<td>0.72&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.68&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.40&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup> Significant at p<0.05, 2-sided.

<sup>b</sup> NE = Not reliably estimable.

<sup>c</sup> Kaplan-Meier estimates.

<sup>d</sup> R-CHOP vs. CHOP.

In Study 8, overall survival estimates at 5 years were 58% vs. 46% for R-CHOP and CHOP, respectively.
14.4 Ninety-Minute Infusions in Previously Untreated Follicular NHL and DLBCL

In Study 10, a total of 363 patients with previously untreated follicular NHL (n=113) or DLBCL (n=250) were evaluated in a prospective, open-label, multi-center, single-arm trial for the safety of 90-minute rituximab infusions. Patients with follicular NHL received rituximab 375 mg/m² plus CVP chemotherapy. Patients with DLBCL received rituximab 375 mg/m² plus CHOP chemotherapy. Patients with clinically significant cardiovascular disease were excluded from the study. Patients were eligible for a 90-minute infusion at Cycle 2 if they did not experience a Grade 3-4 infusion-related adverse event with Cycle 1 and had a circulating lymphocyte count ≤ 5000/mm³ before Cycle 2. All patients were pre-medicated with acetaminophen and an antihistamine and received the glucocorticoid component of their chemotherapy prior to Rituxan infusion. The main outcome measure was the development of Grade 3-4 infusion-related reactions on the day of, or day after, the 90-minute infusion at Cycle 2 [See Adverse Reactions (6.1)].

Eligible patients received their Cycle 2 rituximab infusion over 90 minutes as follows: 20% of the total dose given in the first 30 minutes and the remaining 80% of the total dose given over the next 60 minutes [See Dosage and Administration (2.1)]. Patients who tolerated the 90-minute rituximab infusion at Cycle 2 continued to receive subsequent rituximab infusions at the 90-minute infusion rate for the remainder of the treatment regimen (through Cycle 6 or Cycle 8).

The incidence of Grade 3-4 infusion-related reactions at Cycle 2 was 1.1% (95% CI [0.3%, 2.8%]) among all patients, 3.5% (95% CI [1.0%, 8.8%]) for those patients treated with R-CVP, and 0.0% (95% CI [0.0%, 1.5%]) for those patients treated with R-CHOP. For Cycles 2-8, the incidence of Grade 3-4 infusion-related reactions was 2.8% (95% CI [1.3%, 5.0%]). No acute fatal infusion related reactions were observed.

14.5 Chronic Lymphocytic Leukemia (CLL)

The safety and effectiveness of Rituxan were evaluated in two randomized (1:1) multicenter open-label studies comparing FC alone or in combination with Rituxan for up to 6 cycles in patients with previously untreated CLL [Study 11 (n=817)] or previously treated CLL [Study 12 (n=552)]. Patients received fludarabine 25 mg/m²/day and cyclophosphamide 250 mg/m²/day on days 1, 2 and 3 of each cycle, with or without Rituxan. In both studies, seventy-one percent of CLL patients received 6 cycles and 90% received at least 3 cycles of Rituxan-based therapy.

In Study 11, 30% of patients were 65 years or older, 31% were Binet stage C, 45% had B symptoms, more than 99% had ECOG performance status (PS) 0–1, 74% were male, and 100% were White. In Study 12, 44% of patients were 65 years or older, 28% had B symptoms, 82% received a prior alkylating drug, 18% received prior fludarabine, 100% had ECOG PS 0–1, 67% were male and 98% were White.

The main outcome measure in both studies was progression-free survival (PFS), defined as the time from randomization to progression, relapse, or death, as determined by investigators (Study 11) or an independent review committee (Study 12). The investigator assessed results in Study 12 were supportive of those obtained by the independent review committee. Efficacy results are presented in Table 7.
Table 7
Efficacy Results in Studies 11 and 12

<table>
<thead>
<tr>
<th>Study 11* (Previously untreated)</th>
<th>Study 12* (Previously treated)</th>
</tr>
</thead>
<tbody>
<tr>
<td>R-FC N=408 FC N=409</td>
<td>R-FC N=276 FC N=276</td>
</tr>
<tr>
<td>Median PFS (months) 39.8 31.5</td>
<td>26.7 21.7</td>
</tr>
<tr>
<td>Hazard ratio (95% CI) 0.56 (0.43, 0.71)</td>
<td>0.76 (0.6, 0.96)</td>
</tr>
<tr>
<td>P value (Log-Rank test) &lt;0.01</td>
<td>0.02</td>
</tr>
<tr>
<td>Response rate (95% CI) 86% (82, 89)</td>
<td>73% (68, 77)</td>
</tr>
<tr>
<td></td>
<td>54% (48, 60) 45% (37, 51)</td>
</tr>
</tbody>
</table>

*As defined in 1996 National Cancer Institute Working Group guidelines.

Across both studies, 243 of 676 Rituxan-treated patients (36%) were 65 years of age or older and 100 Rituxan-treated patients (15%) were 70 years of age or older. The results of exploratory subset analyses in elderly patients are presented in Table 8.

Table 8
Efficacy Results in Studies 11 and 12 in Subgroups Defined by Age

<table>
<thead>
<tr>
<th>Age subgroup</th>
<th>Study 11</th>
<th>Study 12</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number of Patients</td>
<td>Hazard Ratio for PFS (95% CI)</td>
</tr>
<tr>
<td>Age &lt; 65 yrs</td>
<td>572</td>
<td>0.52 (0.39, 0.70)</td>
</tr>
<tr>
<td>Age ≥ 65 yrs</td>
<td>245</td>
<td>0.62 (0.39, 0.99)</td>
</tr>
<tr>
<td>Age &lt; 70 yrs</td>
<td>736</td>
<td>0.51 (0.39, 0.67)</td>
</tr>
<tr>
<td>Age ≥ 70 yrs</td>
<td>81</td>
<td>1.17 (0.51, 2.66)</td>
</tr>
</tbody>
</table>

* From exploratory analyses.

14.6 Rheumatoid Arthritis (RA)

Reducing the Signs and Symptoms: Initial and Re-Treatment Courses

The efficacy and safety of Rituxan were evaluated in two randomized, double-blind, placebo-controlled studies of adult patients with moderately to severely active RA who had a prior inadequate response to at least one TNF inhibitor. Patients were 18 years of age or older, diagnosed with active RA according to American College of Rheumatology (ACR) criteria, and had at least 8 swollen and 8 tender joints.

In RA Study 1, patients were randomized to receive either Rituxan 2×1000 mg+MTX or placebo+MTX for 24 weeks. Further courses of Rituxan 2×1000 mg+MTX were administered in an open label extension study at a frequency determined by clinical evaluation, but no sooner than 16 weeks after the preceding course of Rituxan. In addition to the intravenous premedication, glucocorticoids were administered orally on a tapering schedule from baseline through Day 14. The proportions of patients achieving ACR 20, 50, and 70 responses at Week 24 of the placebo-controlled period are shown in Table 9.

In RA Study 2, all patients received the first course of Rituxan 2×1000 mg + MTX. Patients who experienced ongoing disease activity were randomized to receive a second course of either Rituxan 2×1000 mg + MTX or placebo + MTX, the majority between Weeks 24–28. The proportions of
patients achieving ACR 20, 50, and 70 responses at Week 24, before the re-treatment course, and at Week 48, after retreatment, are shown in Table 9.

**Table 9**  
ACR Responses in Study 1 and Study 2 (Percent of Patients)  
(Modified Intent-to-Treat Population)

<table>
<thead>
<tr>
<th>Inadequate Response to TNF Antagonists</th>
<th>Study 1</th>
<th>Study 2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo + MTX</td>
<td>Rituxan + MTX</td>
</tr>
<tr>
<td>Response</td>
<td>n = 201</td>
<td>n = 298</td>
</tr>
<tr>
<td>ACR20</td>
<td>18%</td>
<td>51%</td>
</tr>
<tr>
<td>Week 24</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment Difference (Rituxan – Placebo)</td>
<td>(95% CI)</td>
<td>(95% CI)</td>
</tr>
<tr>
<td>ACR50</td>
<td>5%</td>
<td>27%</td>
</tr>
<tr>
<td>Week 24</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment Difference (Rituxan – Placebo)</td>
<td>(95% CI)</td>
<td>(95% CI)</td>
</tr>
<tr>
<td>ACR70</td>
<td>1%</td>
<td>12%</td>
</tr>
<tr>
<td>Week 24</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment Difference (Rituxan – Placebo)</td>
<td>(95% CI)</td>
<td>(95% CI)</td>
</tr>
</tbody>
</table>

* In Study 2, all patients received a first course of Rituxan 2 x 1000 mg. Patients who experienced ongoing disease activity were randomized to receive a second course of either Rituxan 2 x 1000 mg + MTX or placebo + MTX at or after Week 24.

* Since all patients received a first course of Rituxan, no comparison between Placebo + MTX and Rituxan + MTX is made at Week 24.

* For Study 1, weighted difference stratified by region (US, rest of the world) and Rheumatoid Factor (RF) status (positive > 20 IU/mL, negative < 20 IU/mL) at baseline; For Study 2, weighted difference stratified by RF status at baseline and ≥ 20% improvement from baseline in both SJC and TJC at Week 24 (Yes/No).

Improvement was also noted for all components of ACR response following treatment with Rituxan, as shown in Table 10.
Table 10
Components of ACR Response at Week 24 in Study 1
(Modified Intent-to-Treat Population)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Placebo + MTX (n=201)</th>
<th>Rituxan + MTX (n=298)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>Wk 24</td>
</tr>
<tr>
<td>Tender Joint Count</td>
<td>31.0</td>
<td>27.0</td>
</tr>
<tr>
<td>Swollen Joint Count</td>
<td>20.0</td>
<td>19.0</td>
</tr>
<tr>
<td>Physician Global Assessment&lt;sup&gt;a&lt;/sup&gt;</td>
<td>71.0</td>
<td>69.0</td>
</tr>
<tr>
<td>Patient Global Assessment&lt;sup&gt;b&lt;/sup&gt;</td>
<td>73.0</td>
<td>68.0</td>
</tr>
<tr>
<td>Pain&lt;sup&gt;a&lt;/sup&gt;</td>
<td>68.0</td>
<td>68.0</td>
</tr>
<tr>
<td>Disability Index (HAQ)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>2.0</td>
<td>1.9</td>
</tr>
<tr>
<td>CRP (mg/dL)</td>
<td>2.4</td>
<td>2.5</td>
</tr>
</tbody>
</table>

<sup>a</sup> Visual Analogue Scale: 0 = best, 100 = worst.
<sup>b</sup> Disability Index of the Health Assessment Questionnaire: 0 = best, 3 = worst.

The time course of ACR 20 response for Study 1 is shown in Figure 2. Although both treatment groups received a brief course of intravenous and oral glucocorticoids, resulting in similar benefits at Week 4, higher ACR 20 responses were observed for the Rituxan group by Week 8. A similar proportion of patients achieved these responses through Week 24 after a single course of treatment (2 infusions) with Rituxan. Similar patterns were demonstrated for ACR 50 and 70 responses.
Figure 2
Percent of Patients Achieving ACR 20 Response by Visit*
Study 1 (Inadequate Response to TNF Antagonists)

*The same patients may not have responded at each time point.

Radiographic Response

In RA Study 1, structural joint damage was assessed radiographically and expressed as changes in Genant-modified Total Sharp Score (TSS) and its components, the erosion score (ES) and the joint space narrowing (JSN) score. Rituxan + MTX slowed the progression of structural damage compared to placebo + MTX after 1 year as shown in Table 11.
Table 11
Mean Radiographic Change From Baseline to 104 Weeks

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Rituxan 2×1000 mg+MTXb</th>
<th>Placebo+MTXc</th>
<th>Treatment Difference (Placebo – Rituxan)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change during First Year</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TSS</td>
<td>0.66</td>
<td>1.77</td>
<td>1.11 (0.47, 1.75)</td>
<td></td>
</tr>
<tr>
<td>ES</td>
<td>0.44</td>
<td>1.19</td>
<td>0.75 (0.32, 1.19)</td>
<td></td>
</tr>
<tr>
<td>JSN Score</td>
<td>0.22</td>
<td>0.58</td>
<td>0.36 (0.10, 0.62)</td>
<td></td>
</tr>
<tr>
<td>Change during Second Yeara</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TSS</td>
<td>0.48</td>
<td>1.04</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>ES</td>
<td>0.28</td>
<td>0.62</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>JSN Score</td>
<td>0.20</td>
<td>0.42</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

a Based on radiographic scoring following 104 weeks of observation.

b Patients received up to 2 years of treatment with Rituxan + MTX.

c Patients receiving Placebo + MTX. Patients receiving Placebo + MTX could have received re-treatment with Rituxan + MTX from Week 16 onward.

In RA Study 1 and its open-label extension, 70% of patients initially randomized to Rituxan + MTX and 72% of patients initially randomized to placebo + MTX were evaluated radiographically at Year 2. As shown in Table 11, progression of structural damage in Rituxan + MTX patients was further reduced in the second year of treatment.

Following 2 years of treatment with Rituxan + MTX, 57% of patients had no progression of structural damage. During the first year, 60% of Rituxan + MTX treated patients had no progression, defined as a change in TSS of zero or less compared to baseline, compared to 46% of placebo + MTX treated patients. In their second year of treatment with Rituxan + MTX, more patients had no progression than in the first year (68% vs. 60%), and 87% of the Rituxan + MTX treated patients who had no progression in the first year also had no progression in the second year.

Lesser Efficacy of 500 Vs. 1000 mg Treatment Courses for Radiographic Outcomes

RA Study 3 is a randomized, double-blind, placebo-controlled study which evaluated the effect of placebo + MTX compared to Rituxan 2 x 500 mg + MTX and Rituxan 2 x 1000 mg + MTX treatment courses in MTX-naïve RA patients with moderately to severely active disease. Patients received a first course of two infusions of rituximab or placebo on Days 1 and 15. MTX was initiated at 7.5 mg/week and escalated up to 20 mg/week by Week 8 in all three treatment arms. After a minimum of 24 weeks, patients with ongoing disease activity were eligible to receive re-treatment with additional courses of their assigned treatment. After one year of treatment, the proportion of patients achieving ACR 20/50/70 responses were similar in both Rituxan dose groups and were higher than in the placebo group. However, with respect to radiographic scores, only the Rituxan 1000 mg treatment group demonstrated a statistically significant reduction in TSS: a change of 0.36 units compared to 1.08 units for the placebo group, a 67% reduction.

Physical Function Response

RA Study 4 is a randomized, double-blind, placebo-controlled study in adult RA patients with moderately to severely active disease with inadequate response to MTX. Patients were randomized to receive an initial course of Rituxan 500 mg, Rituxan 1000 mg, or placebo in addition to background MTX.
Physical function was assessed at Weeks 24 and 48 using the Health Assessment Questionnaire Disability Index (HAQ-DI). From baseline to Week 24, a greater proportion of Rituxan-treated patients had an improvement in HAQ-DI of at least 0.22 (a minimal clinically important difference) and a greater mean HAQ-DI improvement compared to placebo, as shown in Table 12. HAQ-DI results for the Rituxan 500 mg treatment group were similar to the Rituxan 1000 mg treatment group; however radiographic responses were not assessed (see Dosing Precaution in the Radiographic Responses section above). These improvements were maintained at 48 weeks.

### Table 12
Improvement from Baseline in Health Assessment Questionnaire Disability Index (HAQ-DI) at Week 24 in Study 4

<table>
<thead>
<tr>
<th></th>
<th>Placebo + MTX n=172</th>
<th>Rituxan 2 × 1000 mg + MTX n=170</th>
<th>Treatment Difference (Rituxan – Placebo) (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Improvement from Baseline</td>
<td>0.19</td>
<td>0.42</td>
<td>0.23 (0.11, 0.34)</td>
</tr>
<tr>
<td>Percent of patients with “Improved” score (Change from Baseline ≥ MCID)</td>
<td>48%</td>
<td>58%</td>
<td>11% (0%, 21%)</td>
</tr>
</tbody>
</table>

* MCID for HAQ = 0.22.

\[ \text{Adjusted difference stratified by region (US, rest of the world) and rheumatoid factor (RF) status (positive ≥ 20 IU/mL, negative < 20 IU/mL) at baseline.} \]

14.7 **Granulomatosis with Polyangiitis (GPA) (Wegener’s Granulomatosis) and Microscopic Polyangiitis (MPA)**

A total of 197 patients with active, severe GPA and MPA (two forms of ANCA Associated Vasculidities) were treated in a randomized, double-blind, active-controlled multicenter, non-inferiority study, conducted in two phases – a 6 month remission induction phase and a 12 month remission maintenance phase. Patients were 15 years of age or older, diagnosed with GPA (75% of patients) or MPA (24% of patients) according to the Chapel Hill Consensus conference criteria (1% of the patients had unknown vasculitis type). All patients had active disease, with a Birmingham Vasculitis Activity Score for Granulomatosis with Polyangiitis (BVAS/GPA) ≥ 3, and their disease was severe, with at least one major item on the BVAS/GPA. Ninety-six (49%) of patients had new disease and 101 (51%) of patients had relapsing disease.

Patients in both arms received 1000 mg of pulse intravenous methylprednisolone per day for 1 to 3 days within 14 days prior to initial infusion. Patients were randomized in a 1:1 ratio to receive either Rituxan 375 mg/m² once weekly for 4 weeks or oral cyclophosphamide 2 mg/kg daily for 3 to 6 months in the remission induction phase. Patients were pre-medicated with antihistamine and acetaminophen prior to Rituxan infusion. Following intravenous corticosteroid administration, all patients received oral prednisone (1 mg/kg/day, not exceeding 80 mg/day) with pre-specified tapering. Once remission was achieved or at the end of the 6 month remission induction period, the cyclophosphamide group received azathioprine to maintain remission. The Rituxan group did not receive additional therapy to maintain remission. The main outcome measure for both GPA and MPA patients was achievement of complete remission at 6 months defined as a BVAS/GPA of 0, and off glucocorticoid therapy. The pre-specified non-inferiority margin was a treatment difference of 20%. As shown in Table 13, the study demonstrated non-inferiority of Rituxan to cyclophosphamide for complete remission at 6 months.
Table 13
Percentage of Patients Who Achieved Complete Remission at 6 Months (Intent-to-Treat Population)

<table>
<thead>
<tr>
<th></th>
<th>Rituxan (n=99)</th>
<th>Cyclophosphamide (n=98)</th>
<th>Treatment Difference (Rituxan – Cyclophosphamide)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rate</td>
<td>64%</td>
<td>53%</td>
<td>11%</td>
</tr>
<tr>
<td>95.1% CI</td>
<td>(54%, 73%)</td>
<td>(43%, 63%)</td>
<td>(−3%, 24%)</td>
</tr>
</tbody>
</table>

a non-inferiority was demonstrated because the lower bound was higher than the prespecified non-inferiority margin (−3% > −20%).

b The 95.1% confidence level reflects an additional 0.001 alpha to account for an interim efficacy analysis.

Complete Remission (CR) at 12 and 18 months
In the Rituxan group, 44% of patients achieved CR at 6 and 12 months, and 38% of patients achieved CR at 6, 12, and 18 months. In patients treated with cyclophosphamide (followed by azathioprine for maintenance of CR), 38% of patients achieved CR at 6 and 12 months, and 31% of patients achieved CR at 6, 12, and 18 months.

Retreatment with Rituxan
Based upon investigator judgment, 15 patients received a second course of Rituxan therapy for treatment of relapse of disease activity which occurred between 8 and 17 months after the first course of Rituxan. The limited data preclude any conclusions regarding the efficacy of subsequent courses of Rituxan in patients with GPA and MPA [see Warnings and Precautions (5.14)].

16 HOW SUPPLIED/STORAGE AND HANDLING
Rituxan vials [100 mg/10 mL single-use vials (NDC 50242-051-21) and 500 mg/50 mL single-use vials (NDC 50242-053-06)] are stable at 2°C–8°C (36°F–46°F). Rituxan vials should be protected from direct sunlight. Do not freeze or shake.

17 PATIENT COUNSELING INFORMATION
Patients should be provided the Rituxan Medication Guide and provided an opportunity to read prior to each treatment session. It is important that the patient’s overall health be assessed at each visit and the risks of Rituxan therapy and any questions resulting from the patient’s reading of the Medication Guide be discussed. See FDA approved patient labeling (Medication Guide).

Rituxan is detectable in serum for up to six months following completion of therapy. Individuals of childbearing potential should use effective contraception during treatment and for 12 months after Rituxan therapy.

RITUXAN® [rituximab]
Manufactured by: Genentech, Inc.
A Member of the Roche Group
1 DNA Way
South San Francisco, CA 94080-4990
US License Number 1048

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Read this Medication Guide before you start Rituxan and before each Rituxan infusion. There may be new information. This Medication Guide does not take the place of talking to your doctor about your medical condition or your treatment.

What is the most important information I should know about Rituxan?

Rituxan can cause serious side effects that can lead to death, including:

- **Infusion reactions.** Infusion reactions are the most common side effect of Rituxan treatment. Serious infusion reactions can happen during your infusion or within 24 hours after your infusion of Rituxan. Your doctor should give you medicines before your infusion of Rituxan to decrease your chance of having a severe infusion reaction.

  Tell your doctor or get medical help right away if you get any of these symptoms during or after an infusion of Rituxan:
  - hives (red itchy welts) or rash
  - itching
  - swelling of your lips, tongue, throat or face
  - sudden cough
  - shortness of breath, difficulty breathing, or wheezing
  - weakness
  - dizziness or feel faint
  - palpitations (feel like your heart is racing or fluttering)
  - chest pain

- **Severe skin and mouth reactions.** Tell your doctor or get medical help right away if you get any of these symptoms at anytime during your treatment with Rituxan:
  - painful sores or ulcers on your skin, lips or in your mouth
  - blisters
  - peeling skin
  - rash
  - pustules

- **Hepatitis B virus (HBV) reactivation.** Before Rituxan treatment, your doctor will do blood tests to check for HBV infection. If you have had hepatitis B or are a carrier of hepatitis B virus, receiving Rituxan could cause the virus to become an active infection again. Hepatitis B reactivation may cause serious liver problems including liver failure, and death. You should not receive Rituxan if you have active hepatitis B liver disease. Your doctor will monitor you for hepatitis B infection during and for several months after you stop receiving Rituxan.

- **Progressive Multifocal Leukoencephalopathy (PML).** PML is a rare, serious brain infection caused by a virus. People with weakened immune systems can get PML. Your chance of getting PML may be higher if you are treated with Rituxan alone or with other medicines that weaken your immune system. PML can result in
death or severe disability. There is no known treatment, prevention, or cure for PML.

Tell your doctor right away if you have any of the following symptoms or if anyone close to you notices these symptoms:

- confusion or problems thinking
- loss of balance
- change in the way you walk or talk
- decreased strength or weakness on one side of your body
- blurred vision or loss of vision

See “What are the possible side effects of Rituxan?” for more information about side effects.

What is Rituxan?

Rituxan is a prescription medicine used to treat:

- **Non-Hodgkin’s Lymphoma (NHL):** alone or with other chemotherapy medicines.
- **Chronic Lymphocytic Leukemia (CLL):** with the chemotherapy medicines fludarabine and cyclophosphamide.
- **Rheumatoid Arthritis (RA):** with another prescription medicine called methotrexate, to reduce the signs and symptoms of moderate to severe active RA in adults, after treatment with at least one other medicine called a Tumor Necrosis Factor (TNF) antagonist has been used and did not work well enough.
- **Granulomatosis with Polyangiitis (GPA) (Wegener’s Granulomatosis) and Microscopic Polyangiitis (MPA):** with glucocorticoids, to treat GPA and MPA.

People with serious infections should not receive Rituxan.

It is not known if Rituxan is safe or effective in children.

What should I tell my doctor before receiving Rituxan?

Before receiving Rituxan, tell your doctor if you:

- have had a severe infusion reaction to Rituxan in the past
- have a history of heart problems, irregular heart beat or chest pain
- have lung or kidney problems
- have an infection or weakened immune system.
- have or have had any severe infections including:
  - Hepatitis B virus (HBV)
  - Hepatitis C virus (HCV)
  - Cytomegalovirus (CMV)
  - Herpes simplex virus (HSV)
  - Parvovirus B19
  - Varicella zoster virus (chickenpox or shingles)
  - West Nile Virus
- have had a recent vaccination or are scheduled to receive vaccinations. You should not receive certain vaccines before or after you receive Rituxan. Tell your doctor if anyone in your household is scheduled to receive a vaccination. Some
types of vaccines can spread to people with a weakened immune system, and cause serious problems.

- have taken Rituxan for GPA or MPA in the past.
- have any other medical conditions
- are pregnant or planning to become pregnant. Rituxan may affect the white blood cell counts of your unborn baby. It is not known if Rituxan may harm your unborn baby in other ways.

Women who are able to become pregnant should use effective birth control (contraception) while using Rituxan and for 12 months after you finish treatment. Talk to your doctor about effective birth control.

- are breast-feeding or plan to breast-feed. It is not known if Rituxan passes into your breast milk. You and your doctor should decide the best way to feed your baby if you receive Rituxan.

Tell your doctor about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. Especially tell your doctor if you take or have taken:
- a Tumor Necrosis Factor (TNF) inhibitor medicine
- a Disease Modifying Anti-Rheumatic Drug (DMARD)

If you are not sure if your medicine is one listed above, ask your doctor or pharmacist.

Know the medicines you take. Keep a list of them to show to your doctor and pharmacist when you get a new medicine. Do not take any new medicine without talking with your doctor.

**How will I receive Rituxan?**

- Rituxan is given by infusion through a needle placed in a vein (intravenous infusion), in your arm. Talk to your doctor about how you will receive Rituxan.
- Your doctor may prescribe medicines before each infusion of Rituxan to reduce side effects of infusions such as fever and chills.
- Your doctor should do regular blood tests to check for side effects to Rituxan.

Before each Rituxan treatment, your doctor or nurse will ask you questions about your general health. Tell your doctor or nurse about any new symptoms.

**What are the possible side effects of Rituxan?**

Rituxan can cause serious and life-threatening side effects, including:

See “**What is the most important information I should know about Rituxan?**”

- **Tumor Lysis Syndrome (TLS).** TLS is caused by the fast breakdown of cancer cells. TLS can cause you to have:
  - kidney failure and the need for dialysis treatment
  - abnormal heart rhythm

  Your doctor may do blood tests to check you for TLS. Your doctor may give you medicine to help prevent TLS.

- **Serious infections.** Serious infections can happen during and after treatment with Rituxan, and can lead to death. Rituxan can lower the ability of your immune system to fight infections. Types of serious infections that can happen with Rituxan include bacterial, fungal, and viral infections. After receiving Rituxan, some patients
have developed low levels of certain antibodies in their blood for a long period of time (longer than 11 months). Some of these patients with low antibody levels developed infections. Call your doctor right away if you have any symptoms of infection:

- fever
- cold symptoms, such as runny nose or sore throat that do not go away
- flu symptoms, such as cough, tiredness, and body aches
- earache or headache
- pain during urination
- white patches in the mouth or throat
- cuts, scrapes or incisions that are red, warm, swollen or painful

- **Heart problems.** Rituxan may cause chest pain and irregular heart beats which may need treatment, or your doctor may decide to stop your treatment with Rituxan.

- **Kidney problems,** especially if you are receiving Rituxan for NHL. Your doctor should do blood tests to check how well your kidneys are working.

- **Stomach and Serious bowel problems that can sometimes lead to death.** Bowel problems, including blockage or tears in the bowel can happen if you receive Rituxan with chemotherapy medicines to treat non-Hodgkin’s lymphoma. Tell your doctor right away if you have any stomach area pain during treatment with Rituxan.

- **Low blood cell counts.** Your doctor may do blood tests during treatment with Rituxan to check your blood cell counts.
  - **White blood cells.** White blood cells fight against bacterial infections. Low white blood cells can cause you to get infections, which may be serious. See “Increased risk of infections” above for a list of symptoms of infection.
  - **Red blood cells.** Red blood cells carry oxygen to your body tissues and organs.
  - **Platelets.** Platelets are blood cells that help your blood to clot.

**Common side effects during Rituxan treatment include:**

- infusion reactions (see "What is the most important information I should know about Rituxan?")
- chills
- infections
- body aches
- tiredness
- low white blood cells

Other side effects with Rituxan include:

- aching joints during or within hours of receiving an infusion
- more frequent upper respiratory tract infection

Tell your doctor about any side effect that bothers you or that does not go away. These are not all of the possible side effects with Rituxan. For more information, ask your doctor or pharmacist.
Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

**General information about Rituxan**

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. This Medication Guide provides a summary of the most important information about Rituxan. If you would like more information, talk with your doctor. You can ask your doctor for information about Rituxan that is written for healthcare professionals.

For more information, go to www.Rituxan.com or call 1-877-474-8892.

**What are the ingredients in Rituxan?**

Active ingredient: rituximab

Inactive ingredients: polysorbate 80, sodium chloride, sodium citrate dihydrate, and water for injection.

This Medication Guide has been approved by the U.S. Food and Drug Administration.

Manufactured by:
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A Member of the Roche Group
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US License Number 1048

Jointly Marketed by: Biogen Inc. and Genentech USA, Inc.

Revised: April 2016

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HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use RITUXAN HYCELA safely and effectively. See full prescribing information for RITUXAN HYCELA.

RITUXAN HYCELA™ (rituximab and hyaluronidase human) injection, for subcutaneous use

Initial U.S. Approval: 2017

WARNING: SEVERE MUCOCUTANEOUS REACTIONS, HEPATITIS B VIRUS REACTIVATION and PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY
See full prescribing information for complete boxed warning.

• Severe mucocutaneous reactions, some with fatal outcomes (5.1).
• Hepatitis B virus reactivation, in some cases resulting in fulminant hepatitis, hepatic failure, and death (5.2).
• Progressive multifocal leukencephalopathy resulting in death (5.3).

INDICATIONS AND USAGE
RITUXAN HYCELA is a combination of rituximab, a CD20-directed cytolytic antibody, and hyaluronidase human, an endoglycosidase, indicated for the treatment of adult patients with:

• Follicular Lymphoma (FL) (1.1)
  o Relapsed or refractory, follicular lymphoma as a single agent
  o Previously untreated follicular lymphoma in combination with first line chemotherapy and, in patients achieving a complete or partial response to rituximab in combination with chemotherapy, as single-agent maintenance therapy
  o Non-progressing (including stable disease), follicular lymphoma as a single agent after first-line cyclophosphamide, vincristine, and prednisone (CVP) chemotherapy
• Diffuse Large B-cell Lymphoma (DLBCL) (1.2)
  o Previously untreated diffuse large B-cell lymphoma in combination with cyclophosphamide, doxorubicin, vincristine, prednisone (CHOP) or other anthracycline-based chemotherapy regimens
• Chronic Lymphocytic Leukemia (CLL) (1.3)
  o Previously untreated and previously treated CLL in combination with fludarabine and cyclophosphamide (FC)

Limitations of Use:
• Initiate treatment with RITUXAN HYCELA only after patients have received at least one full dose of a rituximab product by intravenous infusion. (1.4, 2.1. 5.4).
• RITUXAN HYCELA is not indicated for the treatment of non-malignant conditions. (1.4)

DOSAGE AND ADMINISTRATION
• For subcutaneous use only (2.1)
  • All patients must receive at least one full dose of a rituximab product by intravenous infusion before receiving RITUXAN HYCELA by subcutaneous injection (2.1).
  • FL/DLBCL: Administer 1,400 mg/23,400 Units (1,400 mg rituximab and 23,400 Units hyaluronidase human) subcutaneously according to recommended schedule (2.2, 2.3).
  • CLL: Administer 1,600 mg/26,800 Units (1,600 mg rituximab and 26,800 Units hyaluronidase human) subcutaneously according to recommended schedule (2.4).
• Premedicate with acetaminophen and antihistamine before each dose; In addition, consider premedication with glucocorticoids (2.5, 5.4)
• Administer specified volume into subcutaneous tissue of abdomen; (2.6)
  o 11.7 mL from 1,400 mg/23,400 Units vial over approximately 5 minutes.
  o 13.4 mL from 1,600 mg/26,800 Units vial over approximately 7 minutes.
  o Observe 15 minutes following administration

DOSE FORMS AND STRENGTHS
Injection: (3)
• 1,400 mg rituximab and 23,400 Units hyaluronidase human per 11.7 mL (120 mg/2,000 Units per mL) solution in a single-dose vial
• 1,600 mg rituximab and 26,800 Units hyaluronidase human per 13.4 mL (120 mg/2,000 Units per mL) solution in a single-dose vial

CONTRAINDICATIONS
None. (4)

WARNINGS AND PRECAUTIONS
• Hypersensitivity and other administration reactions: Local cutaneous reactions may occur more than 24 hours after administration. Interrupt injection if severe reaction develops. Premedicate before injection. (5.4)
• Tumor lysis syndrome: Administer aggressive intravenous hydration, anti hyperuricemic agents, monitor renal function. (5.5)
• Infections: Withhold and institute appropriate anti-infective therapy. (5.6)
• Cardiac adverse reactions: Discontinue in case of serious or life-threatening events. (5.7)
• Renal toxicity: Discontinue in patients with rising serum creatinine or oliguria. (5.8)
• Bowel obstruction and perforation: Consider and evaluate for abdominal pain, vomiting, or related symptoms. (5.9)
• Immunizations: Live virus vaccinations prior to or during treatment not recommended. (5.10)
• Embryo-Fetal toxicity: Can cause neonatal harm. Advise of potential risk to neonates and use of effective contraception. (5.11)

ADVERSE REACTIONS
Most common adverse reactions (incidence of ≥ 20%) are: (6.1)
• FL: infections, neutropenia, nausea, constipation, cough, and fatigue
• DLBCL: infections, neutropenia, alopecia, nausea, and anemia
• CLL: infections, neutropenia, nausea, thrombocytopenia, pyrexia, vomiting, and injection site erythema

To report SUSPECTED ADVERSE REACTIONS, contact Genentech at 1-888-835-2555 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS
Renal toxicity when used in combination with cisplatin. (5.8)

USE IN SPECIFIC POPULATIONS
• Lactation: Advise not to breastfeed. (8.2)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 6/2017
FULL PRESCRIBING INFORMATION: CONTENTS*

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FULL PRESCRIBING INFORMATION

WARNING: SEVERE MUCOCUTANEOUS REACTIONS, HEPATITIS B VIRUS REACTIVATION and PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY

Severe Mucocutaneous Reactions
Severe, including fatal, mucocutaneous reactions can occur in patients receiving rituximab-containing products, including RITUXAN HYCELA [see Warnings and Precautions (5.1)].

Hepatitis B Virus (HBV) Reactivation
HBV reactivation can occur in patients treated with rituximab-containing products, including RITUXAN HYCELA, in some cases resulting in fulminant hepatitis, hepatic failure, and death. Screen all patients for HBV infection before treatment initiation, and monitor patients during and after treatment with RITUXAN HYCELA. Discontinue RITUXAN HYCELA and concomitant medications in the event of HBV reactivation [see Warnings and Precautions (5.2)].

Progressive Multifocal Leukoencephalopathy (PML), including fatal PML, can occur in patients receiving rituximab-containing products, including RITUXAN HYCELA [see Warnings and Precautions (5.3) and Adverse Reactions (6.1)].

1 INDICATIONS AND USAGE
1.1 Follicular Lymphoma (FL)
RITUXAN HYCELA is indicated for the treatment of adult patients with:
- Relapsed or refractory, follicular lymphoma as a single agent.
- Previously untreated follicular lymphoma in combination with first-line chemotherapy and, in patients achieving a complete or partial response to rituximab in combination with chemotherapy, as single-agent maintenance therapy.
- Non-progressing (including stable disease), follicular lymphoma as a single agent after first-line cyclophosphamide, vincristine, and prednisone (CVP) chemotherapy.

1.2 Diffuse Large B-Cell Lymphoma (DLBCL)
RITUXAN HYCELA is indicated for the treatment of adult patients with previously untreated diffuse large B-cell lymphoma in combination with cyclophosphamide, doxorubicin, vincristine, prednisone (CHOP) or other anthracycline-based chemotherapy regimens.

1.3 Chronic Lymphocytic Leukemia (CLL)
RITUXAN HYCELA is indicated, in combination with fludarabine and cyclophosphamide (FC), for the treatment of adult patients with previously untreated and previously treated CLL.

1.4 Limitations of Use
- Initiate treatment with RITUXAN HYCELA only after patients have received at least one full dose of a rituximab product by intravenous infusion [see Dosage and Administration (2.1) and Warnings and Precautions (5.4)].
- RITUXAN HYCELA is not indicated for the treatment of non-malignant conditions.

2 DOSAGE AND ADMINISTRATION
2.1 Important Dosing Information
RITUXAN HYCELA is for subcutaneous use only. RITUXAN HYCELA should only be administered by a healthcare professional with appropriate medical support to manage severe reactions that can be fatal if they occur.
All patients must first receive at least one full dose of a rituximab product by intravenous infusion without experiencing severe adverse reactions before starting treatment with RITUXAN HYCELA. If patients are not able to receive one full dose by intravenous infusion, they should continue subsequent cycles with a rituximab product by intravenous infusion and not switch to RITUXAN HYCELA until a full intravenous dose is successfully administered [see Warnings and Precautions (5.4)].

Refer to the prescribing information for a rituximab product for intravenous infusion for additional information.

Premedicate before each dose of RITUXAN HYCELA [see Dosage and Administration (2.5)].

Dose reductions of RITUXAN HYCELA are not recommended. When RITUXAN HYCELA is given in combination with chemotherapy dose, reduce the chemotherapeutic drugs to manage adverse reactions.

2.2 Recommended Dose for Follicular Lymphoma (FL)

All patients must receive at least one full dose of a rituximab product by intravenous infusion before starting treatment with RITUXAN HYCELA [see Dosage and Administration (2.1) and Warnings and Precautions (5.4)]. Premedicate before each dose [see Dosage and Administration (2.5)].

The recommended dose is RITUXAN HYCELA 1,400 mg/23,400 Units (1,400 mg rituximab and 23,400 Units hyaluronidase human) subcutaneously at a fixed dose irrespective of patient’s body surface area according to the following schedules:

- **Relapsed or Refractory, Follicular Lymphoma**
  Administer once weekly for 3 or 7 weeks following a full dose of a rituximab product by intravenous infusion at week 1 (i.e., 4 or 8 weeks in total).

- **Retreatment for Relapsed or Refractory, Follicular Lymphoma**
  Administer once weekly for 3 weeks following a full dose of a rituximab product by intravenous infusion at week 1 (i.e., 4 weeks in total).

- **Previously Untreated, Follicular Lymphoma**
  Administer on Day 1 of Cycles 2–8 of chemotherapy (every 21 days), for up to 7 cycles following a full dose of a rituximab product by intravenous infusion on Day 1 of Cycle 1 of chemotherapy (i.e., up to 8 cycles in total). In patients with complete or partial response, initiate RITUXAN HYCELA maintenance treatment 8 weeks following completion of RITUXAN HYCELA in combination with chemotherapy. Administer RITUXAN HYCELA as a single-agent every 8 weeks for 12 doses.

- **Non-progressing, Follicular Lymphoma after first line CVP chemotherapy**
  Following completion of 6–8 cycles of CVP chemotherapy and a full dose of a rituximab product by intravenous infusion at week 1, administer once weekly for 3 weeks (i.e., 4 weeks in total) at 6 month intervals to a maximum of 16 doses.

2.3 Recommended Dose for Diffuse Large B-Cell Lymphoma (DLBCL)

All patients must receive at least one full dose of a rituximab product by intravenous infusion in combination with CHOP chemotherapy before starting treatment with RITUXAN HYCELA [see Dosage and Administration (2.1) and Warnings and Precautions (5.4)]. Premedicate before each dose [see Dosage and Administration (2.5)].

The recommended dose for DLBCL is RITUXAN HYCELA 1,400 mg/23,400 Units (1,400 mg rituximab and 23,400 Units hyaluronidase human) at a fixed dose irrespective of patient’s body surface area in combination with CHOP chemotherapy. Administer RITUXAN HYCELA 1,400 mg/23,400 Units on Day 1 of Cycles 2–8 of CHOP chemotherapy for up to 7 cycles.
following a full dose of a rituximab product by intravenous infusion at Day 1, Cycle 1 of CHOP chemotherapy (i.e., up to 6–8 cycles in total).

2.4 **Recommended Dose for Chronic Lymphocytic Leukemia (CLL)**

All patients must receive at least one full dose of a rituximab product by intravenous infusion in combination with FC chemotherapy before starting treatment with RITUXAN HYCELA [see Dosage and Administration (2.1) and Warnings and Precautions (5.4)]. Premedicate before each dose [see Dosage and Administration (2.5)].

The recommended dose for CLL is RITUXAN HYCELA 1,600 mg/26,800 Units (1,600 mg rituximab and 26,800 Units hyaluronidase human) in combination with FC chemotherapy, at a fixed dose, irrespective of patient’s body surface area. Administer RITUXAN HYCELA 1,600 mg/26,800 Units on Day 1 of Cycles 2–6 (every 28 days) for a total of 5 cycles following a full intravenous dose at Day 1, Cycle 1 (i.e., 6 cycles in total).

2.5 **Recommended Premedication and Prophylactic Medications**

Premedicate with acetaminophen and an antihistamine before each dose of RITUXAN HYCELA. Premedication with a glucocorticoid should also be considered [see Dosage and Administration (2.2, 2.3, 2.4)].

Provide prophylaxis for Pneumocystis jiroveci pneumonia (PCP) and herpes virus infections for patients with CLL during treatment and for up to 12 months following treatment as appropriate [see Warnings and Precautions (5.6)].

2.6 **Administration and Storage**

RITUXAN HYCELA is ready to use. To avoid needle clogging, attach the hypodermic injection needle to the syringe immediately prior to administration. RITUXAN HYCELA is compatible with polypropylene and polycarbonate syringe material and stainless steel transfer and injection needles. Use the product immediately.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration. RITUXAN HYCELA should be a clear to opalescent and colorless to yellowish liquid. Do not use vial if particulates or discoloration is present.

**Administration**

- Inject RITUXAN HYCELA into the subcutaneous tissue of the abdomen over approximately 5–7 minutes and never inject into areas where the skin is red, bruised, tender or hard, or areas where there are moles or scars. No data are available on performing the injection at other sites of the body.
- Inject 11.7 mL of RITUXAN HYCELA 1,400 mg/23,400 Units vial (1,400 mg rituximab and 23,400 Units hyaluronidase human) subcutaneously into the abdomen over approximately 5 minutes.
- Inject 13.4 mL of RITUXAN HYCELA 1,600 mg/26,800 Units vial (1,600 mg rituximab and 26,800 Units hyaluronidase human) subcutaneously into the abdomen over approximately 7 minutes.

If administration of RITUXAN HYCELA is interrupted, continue administering at the same site, or at a different site, but restricted to the abdomen.

Observe patients for at least 15 minutes following RITUXAN HYCELA administration [see Warnings and Precautions (5.4)].

During treatment with RITUXAN HYCELA, do not administer other medications for subcutaneous use at the same sites as RITUXAN HYCELA.

**Storage**
After the solution of RITUXAN HYCELA is withdrawn from the vial, it should be labeled with the peel-off sticker and used immediately. If not used immediately, prepare in controlled and validated aseptic conditions. Once transferred from the vial into the syringe, store the solution of RITUXAN HYCELA in the refrigerator at 2°C–8°C (36°F–46°F) up to 48 hours and subsequently for 8 hours at room temperature up to 30°C (86°F) in diffuse light.

3 DOSAGE FORMS AND STRENGTHS

RITUXAN HYCELA is a colorless to yellowish, clear to opalescent solution for subcutaneous injection:

- Injection: 1,400 mg rituximab and 23,400 Units hyaluronidase human per 11.7 mL (120 mg/2,000 Units per mL) in a single-dose vial.
- Injection: 1,600 mg rituximab and 26,800 Units hyaluronidase human per 13.4 mL (120 mg/2,000 Units per mL) in a single-dose vial.

4 CONTRAINDICATIONS

None

5 WARNINGS AND PRECAUTIONS

5.1 Severe Mucocutaneous Reactions

Mucocutaneous reactions, some with fatal outcome, can occur in patients treated with rituximab-containing products, including RITUXAN HYCELA. These reactions include paraneoplastic pemphigus, Stevens-Johnson syndrome, lichenoid dermatitis, vesiculobullous dermatitis, and toxic epidermal necrolysis. Discontinue RITUXAN HYCELA in patients who experience a severe mucocutaneous reaction. The safety of re-administration of a rituximab-containing product, including RITUXAN HYCELA, to patients with severe mucocutaneous reactions has not been determined.

5.2 Hepatitis B Virus Reactivation

Hepatitis B virus (HBV) reactivation, in some cases resulting in fulminant hepatitis, hepatic failure and death, can occur in patients treated with drugs classified as CD20-directed cytolytic antibodies, including rituximab-containing products. HBV reactivation is defined as an abrupt increase in HBV replication manifesting as a rapid increase in serum HBV DNA levels or detection of HBsAg in a person who was previously HBsAg negative and anti-HBc positive. Reactivation of HBV replication is often followed by hepatitis, i.e., increase in transaminase levels. In severe cases increase in bilirubin levels, liver failure, and death can occur.

Screen all patients for HBV infection by measuring HBsAg and anti-HBc before initiating treatment with a rituximab-containing product. For patients who show evidence of prior hepatitis B infection (HBsAg positive [regardless of antibody status] or HBsAg negative but anti-HBc positive), consult with physicians with expertise in managing hepatitis B regarding monitoring and consideration for HBV antiviral therapy before and/or during treatment with a rituximab-containing product. Monitor patients with evidence of current or prior HBV infection for clinical and laboratory signs of hepatitis or HBV reactivation during and for several months following RITUXAN HYCELA. HBV reactivation has been reported up to 24 months following completion of therapy containing rituximab.

In patients who develop reactivation of HBV while on RITUXAN HYCELA, immediately discontinue treatment and any concomitant chemotherapy, and institute appropriate treatment. Insufficient data exist regarding the safety of resuming RITUXAN HYCELA treatment in patients who develop HBV reactivation. Resumption of RITUXAN HYCELA treatment in patients whose HBV reactivation resolves should be discussed with physicians with expertise in managing HBV.
5.3 Progressive Multifocal Leukoencephalopathy (PML)
JC virus infection resulting in PML and death has been observed in patients receiving rituximab-containing products, including RITUXAN HYCELA. Consider the diagnosis of PML in any patient presenting with new-onset neurologic manifestations. Evaluation of PML includes, but is not limited to, consultation with a neurologist, brain MRI, and lumbar puncture.

Discontinue RITUXAN HYCELA and consider discontinuation or reduction of any concomitant chemotherapy or immunosuppressive therapy in patients who develop PML [see Adverse Reactions (6.1)].

5.4 Hypersensitivity and other Administration Reactions

Systemic Reactions
Patients must receive at least one full dose of a rituximab product by intravenous infusion before receiving RITUXAN HYCELA due to the higher risk of hypersensitivity and other acute reactions during the first infusion [see Dosage and Administration (2.1)]. Beginning therapy with a rituximab product by intravenous infusion allows management of hypersensitivity and other administration reactions by slowing or stopping the intravenous infusion.

Rituximab-containing products, including RITUXAN HYCELA, are associated with hypersensitivity and other administration reactions, which may be related to release of cytokines and/or other chemical mediators. Cytokine release syndrome may be clinically indistinguishable from acute hypersensitivity reactions.

This set of reactions which includes syndrome of cytokine release, tumor lysis syndrome and anaphylactic and hypersensitivity reactions are described below. They are not specifically related to the route of administration of a rituximab-containing product.

Severe infusion-related reactions with fatal outcome have been reported with the use of intravenous formulations of rituximab products, with an onset ranging within 30 minutes to 2 hours after starting the first intravenous infusion. They were characterized by pulmonary events in addition to fever, chills, rigors, hypotension, urticaria, angioedema and other symptoms.

Anaphylactic and other hypersensitivity reactions can also occur. In contrast to cytokine release syndrome, true hypersensitivity reactions typically occur within minutes after starting infusion.

Severe cytokine release syndrome is characterized by severe dyspnea, often associated by bronchospasm and hypoxia, in addition to fever, chills, rigors, urticaria, and angioedema. This syndrome may be associated with acute respiratory failure and death [see Warnings and Precautions (5.5)]. Cytokine release syndrome may occur within 1–2 hours of initiating the infusion. Patients with a history of pulmonary insufficiency or those with pulmonary tumor infiltration may be at a greater risk of poor outcome. Rituximab product administration should be interrupted immediately and aggressive symptomatic treatment initiated.

During RITUXAN HYCELA administration, the injection should be interrupted immediately when observing signs of a severe reaction and aggressive symptomatic treatment should be initiated.

Closely monitor the following patients: those with pre-existing cardiac or pulmonary conditions, those who experienced prior cardiopulmonary adverse reactions, and those with high numbers of circulating malignant cells (≥ 25,000/mm$^3$) [see Warnings and Precautions (5.5, 5.7)].

Premedicate patients with an antihistamine and acetaminophen prior to each administration of RITUXAN HYCELA [see Dosage and Administration (2.5)]. Premedication with glucocorticoids should also be considered. Observe patients for at least 15 minutes following RITUXAN HYCELA. A longer period may be appropriate in patients with an increased risk of hypersensitivity reactions.
Local Cutaneous Reactions

Local cutaneous reactions, including injection site reactions, have been reported in patients receiving RITUXAN HYCELA. Symptoms included pain, swelling, induration, hemorrhage, erythema, pruritus, and rash [see Adverse Reactions (6.1)]. Some local cutaneous reactions occurred more than 24 hours after RITUXAN HYCELA administration. The incidence of local cutaneous reactions following administration of RITUXAN HYCELA was 16%. Reactions were mild or moderate and resolved without any specific treatment. Local cutaneous reactions of any Grade were most common during the first RITUXAN HYCELA cycle (Cycle 2; 5%) with the incidence decreasing with subsequent injections.

5.5 Tumor Lysis Syndrome (TLS)
TLS can occur within 12–24 hours after administration of a rituximab-containing product, including RITUXAN HYCELA. A high number of circulating malignant cells (≥ 25,000/mm³) or high tumor burden confers a greater risk of TLS. Administer aggressive intravenous hydration and anti-hyperuricemic therapy in patients at high risk for TLS. Correct electrolyte abnormalities, monitor renal function and fluid balance, and administer supportive care, including dialysis as indicated [see Warnings and Precautions (5.8)].

5.6 Infections
Serious, including fatal, bacterial, fungal, and new or reactivated viral infections can occur during and following the completion of therapy with rituximab-containing products, including RITUXAN HYCELA. The incidence of infections with RITUXAN HYCELA vs rituximab was 56% and 49% respectively in patients with CLL, and 46% and 41% respectively in patients with FL/DLBCL in combination with chemotherapy. Infections have been reported in some patients with prolonged hypogammaglobulinemia (defined as hypogammaglobulinemia > 11 months after rituximab exposure). New or reactivated viral infections included cytomegalovirus, herpes simplex virus, parvovirus B19, varicella zoster virus, West Nile virus, and hepatitis B and C. Discontinue RITUXAN HYCELA for serious infections and institute appropriate anti-infective therapy [see Adverse Reactions (6.1)].

5.7 Cardiovascular Adverse Reactions
Cardiac adverse reactions, including ventricular fibrillation, myocardial infarction, and cardiogenic shock may occur with rituximab-containing products, including RITUXAN HYCELA.

Discontinue RITUXAN HYCELA for serious or life threatening cardiac arrhythmias. Perform cardiac monitoring during and after all administrations of RITUXAN HYCELA for patients who develop clinically significant arrhythmias, or who have a history of arrhythmia or angina [see Adverse Reactions (6.1)].

5.8 Renal Toxicity
Severe, including fatal, renal toxicity can occur after administration of rituximab-containing products, including RITUXAN HYCELA. Renal toxicity has occurred in patients who experience tumor lysis syndrome and in patients with administered concomitant cisplatin therapy during clinical trials. The combination of cisplatin and RITUXAN HYCELA is not an approved treatment regimen. Monitor closely for signs of renal failure and discontinue RITUXAN HYCELA in patients with a rising serum creatinine or oliguria [see Warnings and Precautions (5.5)].

5.9 Bowel Obstruction and Perforation
Abdominal pain, bowel obstruction and perforation, in some cases leading to death, can occur in patients receiving rituximab-containing products, including RITUXAN HYCELA, in combination with chemotherapy. In postmarketing reports, the mean time to documented
gastrointestinal perforation was 6 (range 1–77) days. Evaluate if symptoms of obstruction such as abdominal pain or repeated vomiting occur.

5.10 Immunization
The safety of immunization with live viral vaccines following rituximab-containing products, including RITUXAN HYCELA, therapy has not been studied and vaccination with live virus vaccines is not recommended before or during treatment.

5.11 Embryo-Fetal Toxicity
Based on human data, rituximab-containing products can cause fetal harm due to B-cell lymphocytopenia in infants exposed to rituximab in-utero. Advise pregnant women of the risk to a fetus. Females of childbearing potential should use effective contraception while receiving RITUXAN HYCELA and for 12 months following the last dose of rituximab-containing products, including RITUXAN HYCELA.

6 ADVERSE REACTIONS
The following serious adverse reactions are discussed in greater detail in other sections of the labeling:

- Mucocutaneous reactions [see Warnings and Precautions (5.1)]
- Hepatitis B reactivation including fulminant hepatitis [see Warnings and Precautions (5.2)]
- Progressive multifocal leukoencephalopathy [see Warnings and Precautions (5.3)]
- Hypersensitivity and other administration reactions [see Warnings and Precautions (5.4)]
- Tumor lysis syndrome [see Warnings and Precautions (5.5)]
- Infections [see Warnings and Precautions (5.6)]
- Cardiac arrhythmias [see Warnings and Precautions (5.7)]
- Renal toxicity [see Warnings and Precautions (5.8)]
- Bowel obstruction and perforation [see Warnings and Precautions (5.9)]

6.1 Clinical Trials Experience
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

The data described below reflect exposure to RITUXAN HYCELA in 892 patients in four controlled trials with exposures ranging from a single injection up to 27 months of treatment.

The population included 382 patients with follicular lymphoma (FL), 369 patients with diffuse large B-cell lymphoma (DLBCL), and 141 patients with chronic lymphocytic leukemia (CLL). The population was aged 18–85 years (with a median age of 60 years), 53% male and 47% female. Most of the patients were Caucasians (84%). In the SABRINA study patients with FL received a full dose of a rituximab product by intravenous infusion, followed by RITUXAN HYCELA (1,400 mg rituximab/23,400 Units hyaluronidase human), in combination with chemotherapy for up to 7 doses (i.e., total of 8 doses in combination with chemotherapy), or as monotherapy for up to 12 doses (maintenance treatment). In the MabEase study patients with DLBCL received a full dose of a rituximab product by intravenous infusion, followed by RITUXAN HYCELA (1,400 mg rituximab/23,400 Units hyaluronidase human), given in combination with chemotherapy for up to 7 doses (i.e., up to a total of 8 doses). In the SAWYER study patients with CLL on part 2 received a full dose of a rituximab product by intravenous infusion, followed by RITUXAN HYCELA (1,600 mg rituximab/26,800 Units hyaluronidase human) for up to 5 doses, in combination with fludarabine and cyclophosphamide (i.e., total of 6 doses).
The most common adverse reactions (≥ 20%) of RITUXAN HYCELA observed in patients with FL on the SABRINA study were: infections, neutropenia, nausea, constipation, cough, and fatigue.

The most common adverse reactions (≥ 20%) of RITUXAN HYCELA observed in patients with DLBCL on the MabEase study were: infections, neutropenia, alopecia, nausea, and anemia.

The most common adverse reactions (≥ 20%) of RITUXAN HYCELA observed in patients with CLL on part 2 of the SAWYER study were: infections, neutropenia, nausea, thrombocytopenia, pyrexia, vomiting, and injection site erythema.

Administration-related reactions (ARRs)
Administration-related reactions (ARRs) with RITUXAN HYCELA were defined as all the adverse reactions related to the administration of RITUXAN HYCELA within the 24 hours post injection.

The incidence of ARRs with RITUXAN HYCELA was 34% in FL/DLBCL in combination with chemotherapy with injection site erythema (5%), chills (3%), dyspnea, erythema, flushing, injection site pain, nausea, pruritus, pyrexia, rash, and throat irritation (2% each) being the most common ARRs. The incidence of ARRs in FL maintenance setting was 20%. The most common ARRs were injection site erythema (7%), erythema (4%), injection site pain/edema, myalgia, and rash (2% each).

The incidence of ARRs with RITUXAN HYCELA in CLL was 44%.

With the exception of Local Cutaneous Reactions, the incidence and profile of adverse reactions reported for RITUXAN HYCELA were comparable with those for rituximab. The overall incidence of adverse reactions for intravenous rituximab versus RITUXAN HYCELA in combination with chemotherapy for FL/DLBCL was 93% versus 95% (BSA ≤ 1.73 m²), 89% versus 93% (1.73 < BSA ≤ 1.92 m²), and 94% versus 94% (BSA > 1.92 m²). The overall incidence of adverse reactions for rituximab versus RITUXAN HYCELA in CLL was 89% versus 100% (BSA ≤ 1.81 m²), 97% versus 88% (1.82 < BSA ≤ 1.99 m²), and 88% versus 93% (BSA > 2.00 m²).

Summary of Clinical Trial Experience in Follicular Lymphoma (FL)
The data in Table 1 were obtained in the SABRINA study, a two-stage randomized, controlled study in patients with previously untreated FL. The study compared patients receiving RITUXAN HYCELA (1,400 mg rituximab/23,400 Units hyaluronidase human; n=197) with patients receiving a rituximab product by intravenous infusion (375 mg/m²; n=210), both in combination with CHOP or CVP followed by maintenance treatment with RITUXAN HYCELA or a rituximab product by intravenous infusion.

The majority of patients completed all 8 cycles of combination treatment with chemotherapy (91% RITUXAN HYCELA vs. 90% rituximab). In addition, 69% of patients in each of the treatment groups completed all 20 cycles of combination plus maintenance treatment. In both RITUXAN HYCELA and rituximab groups, patients experienced similar median duration of exposure (27.1 months for each arm).

Across the two stages, the overall demographics and baseline characteristics were balanced between the treatment groups. However, there were more female patients (53%) randomized in the study than male patients (47%) and a higher proportion of females were randomized to receive RITUXAN HYCELA (59% female) compared with the rituximab group (48%). The treatment groups in the combined Stage 1 and 2 population were otherwise balanced in regard to baseline demographics, characterized by a median age of 57 years (56.0 years [range 28–85 years] for RITUXAN HYCELA and 57 years [range 28–86 years] for rituximab) and median BSA of 1.83 m² (1.80 and 1.84 m² for RITUXAN HYCELA and rituximab, respectively).
The incidence of all adverse reactions was 96% for RITUXAN HYCELA vs. 95% for rituximab (Table 1). Grade 3–4 adverse reactions were reported in 55% of patients receiving RITUXAN HYCELA vs. 53% in patients receiving rituximab. Serious adverse reactions were reported in 37% of patients receiving RITUXAN HYCELA vs. 34% of patients receiving rituximab. The most common adverse reactions (occurring in ≥ 20% of patients in any arm) were infections, neutropenia, nausea, constipation, cough, and fatigue.

A total of 36 patients died, including 14/197 patients (7%) who received RITUXAN HYCELA and 22/210 patients (10%) who received rituximab. Of these 36 patients, 19 patients (7 patients RITUXAN HYCELA [4%] vs. 12 patients rituximab [6%]) died due to adverse reactions and 13 patients (6 patients RITUXAN HYCELA [3%] vs. 7 patients rituximab [3%]) died due to disease progression.

The incidence of administration-related reactions (ARRs) due to the subcutaneous route of administration associated with RITUXAN HYCELA was assessed in combination with chemotherapy and during maintenance. Thirty patients (15%) experienced an ARR during the first administration of RITUXAN HYCELA (Cycle 2). Incidence of ARRs generally decreased at subsequent cycles with 18 patients (9%) reporting ARR at Cycle 3, 13 patients (7%) at Cycle 4, 11 patients (6%) at Cycles 5 and 6, 12 patients (7%) at Cycle 7, and 8 patients (4%) at Cycle 8. During RITUXAN HYCELA monotherapy in the maintenance setting the incidence of ARRs at each cycle was ≤ 7% and was observed in 24 patients (14%) overall. Grade 1–2 ARRs constituted 96% of the overall ARRs. Grade 3 ARRs were reported during the first administration of RITUXAN HYCELA at Cycle 2 by 2 patients. Of the reported ARRs, local cutaneous reactions with RITUXAN HYCELA were reported in 32 patients. These events resolved within a median of 2 days from the onset (range 1 to 37 days). Majority of these reactions were Grade 1 and 2 and were observed in 31 patients (16%).
Table 1: Incidence of Adverse Reactions in ≥ 5% of Patients with Previously Untreated Follicular Lymphoma Receiving RITUXAN HYCELA or Rituximab in Combination with CHOP or CVP and as Monotherapy for Maintenance Treatment

<table>
<thead>
<tr>
<th>Body System/Adverse Reactions</th>
<th>RITUXAN HYCELA (n=197)</th>
<th></th>
<th>Rituximab (n=210)</th>
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<tbody>
<tr>
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<td>All AEs</td>
<td>Grade 3–4</td>
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Summary of Clinical Trial Experience in Diffuse Large B-Cell Lymphoma (DLBCL)

The data in Table 2 were obtained in the MabEASE study, a comparative, randomized, parallel-group, multicenter study to investigate the efficacy of RITUXAN HYCELA (1,400 mg rituximab and 23,400 Units hyaluronidase human; n=369) versus 375 mg/m² a rituximab product by intravenous infusion (n=203) both in combination with CHOP (R-CHOP) in previously untreated patients with CD20-positive DLBCL.

Eighty two percent of patients receiving RITUXAN HYCELA or rituximab completed all 8 cycles of study treatment. In both RITUXAN HYCELA and rituximab treatment groups, patients experienced 4.9 months median duration of rituximab exposure in each arm.

The demographic characteristics were balanced between the two treatment groups. Most patients were Caucasian (79%) and more than half (54%) were male. The study population had a median age of 64 years (61% of patients aged ≥ 60 years) with median BSA of 1.83 m² (1.83 and 1.84 m² for RITUXAN HYCELA and rituximab groups, respectively).

The incidences of adverse reactions of any grade (RITUXAN HYCELA [94%] vs. rituximab [92%]) (Table 2), Grade 3–4 adverse reactions (RITUXAN HYCELA [63%] vs. rituximab [57%]), and serious adverse reactions (RITUXAN HYCELA [42%] vs. rituximab [37%]) were generally comparable between the two treatment groups. The common adverse reactions (occurring in ≥ 20% of patients in any treatment group) were neutropenia, alopecia, nausea, and anemia.

A total of 91 patients (16%) died, including 58/369 patients (16%) in RITUXAN HYCELA and 33/203 patients (16%) in rituximab. Of these patients, 44 patients (29 patients RITUXAN HYCELA [8%] vs. 15 patients rituximab [7%]) died due to adverse reactions and 35 patients (22 patients RITUXAN HYCELA [6%] vs. 13 patients rituximab [6%]) died due to disease progression. Pneumonia (4 patients RITUXAN HYCELA vs. 1 patient rituximab), septic shock (2 patients RITUXAN HYCELA vs. 3 patients rituximab), and cardiac arrest (1 patient RITUXAN HYCELA vs. 3 patients rituximab) were the most common adverse reactions leading to death.

The incidence of administration-related reactions was balanced between the RITUXAN HYCELA and rituximab groups (28% vs. 29%). Grade 1–2 ARRs constituted 97% of the overall ARRs for the RITUXAN HYCELA arm and 80% for the rituximab arm. Of the reported ARRs, local cutaneous reactions with RITUXAN HYCELA were reported in 17 patients. These events resolved within a median of 2 days from the onset (range 1 to 32 days). Majority of these reactions were Grade 1 and 2 and were observed in 16 patients (4%).
### Table 2: Incidence of Adverse Reactions in ≥ 5% of Patients with Previously Untreated DLBCL Receiving RITUXAN HYCELA or Rituximab in Combination with CHOP

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<tr>
<th>Body System/Adverse Reactions</th>
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<th>Rituximab + CHOP (n=203)</th>
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<td></td>
<td>All AEs %</td>
<td>Grade 3–4 %</td>
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<tr>
<td>Constipation</td>
<td>15 &lt; 1</td>
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<tr>
<td>Vomiting</td>
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<tr>
<td>Abdominal Pain</td>
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<td>General Disorders and Administration Site</td>
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<tr>
<td>Neuropathy Peripheral</td>
<td>12 &lt; 1</td>
<td></td>
</tr>
<tr>
<td>Paresthesia</td>
<td>9 &lt; 1</td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>6 0</td>
<td></td>
</tr>
<tr>
<td>Skin and Subcutaneous Tissue Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alopecia</td>
<td>24 0</td>
<td></td>
</tr>
<tr>
<td>Respiratory, Thoracic and Mediastinal Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cough</td>
<td>11 &lt; 1</td>
<td></td>
</tr>
<tr>
<td>Dyspnea</td>
<td>6 0</td>
<td></td>
</tr>
<tr>
<td>Psychiatric Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insomnia</td>
<td>7 &lt; 1</td>
<td></td>
</tr>
</tbody>
</table>

### Summary of Clinical Trial Experience in Chronic Lymphocytic Leukemia

The data in Table 3 were obtained in part 2 of the SAWYER study, a two-part, comparative, randomized, parallel-group, multicenter study of RITUXAN HYCELA versus a rituximab product by intravenous infusion both in combination with fludarabine and cyclophosphamide (FC) chemotherapy in patients with previously untreated CLL.

The safety analysis population in part 2 of the study included 85 patients receiving RITUXAN HYCELA (1,600 mg rituximab/26,800 Units hyaluronidase human) and 89 patients receiving
500 mg/m² rituximab. In both RITUXAN HYCELA and rituximab groups, patients had similar median duration of rituximab exposure (4.9 vs. 4.7 months). The majority of patients received all 6 cycles of study treatment (86% RITUXAN HYCELA vs. 81% rituximab).

The patient population was predominantly Caucasian (96%), male (65%), with a median age of 60 years and median BSA of 1.9 m² (1.97 and 1.86 m² for the RITUXAN HYCELA and intravenous rituximab groups, respectively). Overall, the treatment groups were balanced with respect to demographic characteristics, with the exception of more males in the RITUXAN HYCELA arm (71% RITUXAN HYCELA vs. 60% rituximab). Baseline disease characteristics were similar between the two groups. Over half of the patients (62%) had Binet Stage B disease and the majority had typical CLL characterizations (93%), with median time from first CLL diagnosis to randomization being 18.5 months.

The incidences of adverse reactions were balanced between the two treatment groups (96% RITUXAN HYCELA vs. 91% rituximab), and the common adverse reactions (occurring in ≥ 20% of patients in any arm) were infections, neutropenia, nausea, thrombocytopenia, pyrexia, anemia, vomiting, and injection site erythema. The incidences of Grade 3–4 adverse reactions were also balanced between the two treatment groups (69% RITUXAN HYCELA vs. 71% rituximab). The incidence of serious adverse reactions was 29% for RITUXAN HYCELA and 33% for rituximab. The incidence of administration-related reactions was 44% for RITUXAN HYCELA and 45% for rituximab. Of the reported ARRs, local cutaneous reactions with RITUXAN HYCELA were reported in 15 patients. These events resolved within a median of 6 days from the onset (range 3 to 29 days). Majority of these reactions were Grade 1 and 2 and were observed in 14 patients (16%).

A total of 9 patients (5%) died, including 5 patients in the RITUXAN HYCELA group and 4 patients in the rituximab group. In the RITUXAN HYCELA group, 1 patient died due to herpes zoster infection, 1 patient died as a result of progressive multifocal leukoencephalopathy (PML) (considered by the investigator as related to rituximab), and 3 patients died due to disease progression. In the rituximab group, 2 patients died due to diarrhea and listeriosis and 2 patients died due to disease progression.
Table 3: Incidence of Adverse Reactions in ≥ 5% of Patients with Previously Untreated CLL Receiving RITUXAN HYCELA or Rituximab in Combination with FC

<table>
<thead>
<tr>
<th>Body System/Adverse Reactions</th>
<th>RITUXAN HYCELA + FC (n=85)</th>
<th>Rituximab + FC (n=89)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All AEs %</td>
<td>Grade 3–4 %</td>
</tr>
<tr>
<td>Gastrointestinal Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>38</td>
<td>1</td>
</tr>
<tr>
<td>Vomiting</td>
<td>21</td>
<td>2</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>12</td>
<td>0</td>
</tr>
<tr>
<td>Abdominal Pain</td>
<td>9</td>
<td>0</td>
</tr>
<tr>
<td>Constipation</td>
<td>8</td>
<td>0</td>
</tr>
<tr>
<td>General Disorders and Administration Site Conditions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pyrexia</td>
<td>32</td>
<td>5</td>
</tr>
<tr>
<td>Injection Site Erythema</td>
<td>26</td>
<td>2</td>
</tr>
<tr>
<td>Injection Site Pain</td>
<td>16</td>
<td>1</td>
</tr>
<tr>
<td>Chills</td>
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<td>0</td>
</tr>
<tr>
<td>Fatigue</td>
<td>11</td>
<td>0</td>
</tr>
<tr>
<td>Asthenia</td>
<td>8</td>
<td>1</td>
</tr>
<tr>
<td>Infections</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Upper Respiratory Tract Infection</td>
<td>13</td>
<td>0</td>
</tr>
<tr>
<td>Respiratory Tract Infection</td>
<td>8</td>
<td>1</td>
</tr>
<tr>
<td>Bronchitis</td>
<td>7</td>
<td>0</td>
</tr>
<tr>
<td>Urinary Tract Infection</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Blood and Lymphatic System Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutropenia</td>
<td>65</td>
<td>56</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>24</td>
<td>6</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>19</td>
<td>14</td>
</tr>
<tr>
<td>Anemia</td>
<td>13</td>
<td>5</td>
</tr>
<tr>
<td>Febrile Neutropenia</td>
<td>11</td>
<td>8</td>
</tr>
<tr>
<td>Musculoskeletal and Connective Tissue Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arthralgia</td>
<td>9</td>
<td>0</td>
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<tr>
<td>Pain In Extremity</td>
<td>7</td>
<td>1</td>
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<tr>
<td>Bone Pain</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>Nervous System Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>7</td>
<td>0</td>
</tr>
<tr>
<td>Skin and Subcutaneous Tissue Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Erythema</td>
<td>15</td>
<td>0</td>
</tr>
<tr>
<td>Rash</td>
<td>12</td>
<td>0</td>
</tr>
<tr>
<td>Pruritus</td>
<td>8</td>
<td>0</td>
</tr>
<tr>
<td>Respiratory, Thoracic and Mediastinal Disorders</td>
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<td></td>
</tr>
<tr>
<td>Cough</td>
<td>13</td>
<td>0</td>
</tr>
<tr>
<td>Oropharyngeal Pain</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Psychiatric Disorders</td>
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<td></td>
</tr>
<tr>
<td>Insomnia</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Vascular Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypotension</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Hypertension</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>
6.2 Immunogenicity

As with all therapeutic proteins, there is potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to RITUXAN HYCELA and rituximab in the studies described below with the incidence of antibodies in other studies or to other products may be misleading.

In the SABRINA study, where previously untreated patients with follicular lymphoma were treated with RITUXAN HYCELA or rituximab in combination with CVP or CHOP, the incidence of treatment-induced/enhanced anti-rituximab antibodies in the RITUXAN HYCELA group was similar to that observed in the rituximab group (2.0% RITUXAN HYCELA vs. 1.5% rituximab). The incidence of treatment-induced/enhanced anti-recombinant human hyaluronidase antibodies was 13% in the RITUXAN HYCELA group compared with 8% in the rituximab group, and the overall proportion of patients found to have anti-recombinant human hyaluronidase antibodies remained generally constant over the follow-up period in both cohorts. All patients who tested positive for anti-recombinant human hyaluronidase antibodies at any point during the study were negative for neutralizing antibodies.

In the SAWYER study, where previously untreated patients with CLL were treated with RITUXAN HYCELA or rituximab in combination with FC, the incidence of treatment-induced/enhanced anti-rituximab antibodies was 2.4% in the RITUXAN HYCELA group vs. 6.7% in rituximab group. The incidence of treatment-induced/enhanced anti-recombinant human hyaluronidase antibodies was 10.6% in the RITUXAN HYCELA treatment arm. None of the patients who tested positive for anti-recombinant human hyaluronidase antibodies tested positive for neutralizing antibodies.

The clinical relevance of the development of anti-rituximab or anti-recombinant human hyaluronidase antibodies after treatment with RITUXAN HYCELA is not known.

6.3 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of rituximab-containing products. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

- Hematologic: prolonged pancytopenia, marrow hypoplasia, Grade 3–4 prolonged or late-onset neutropenia, hyperviscosity syndrome in Waldenstrom’s macroglobulinemia, prolonged hypogammaglobulinemia
- Cardiac: fatal cardiac failure
- Immune/Autoimmune Events: uveitis, optic neuritis, systemic vasculitis, pleuritis, lupus-like syndrome, serum sickness, polyarticular arthritis, and vasculitis with rash.
- Infection: viral infections, including progressive multifocal leukoencephalopathy (PML), increase in fatal infections in HIV-associated lymphoma, and a reported increased incidence of Grade 3 and 4 infections
- Neoplasia: disease progression of Kaposi’s sarcoma.
- Skin: severe mucocutaneous reactions.
- Gastrointestinal: bowel obstruction and perforation.
- Pulmonary: fatal bronchiolitis obliterans and fatal interstitial lung disease.
8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on human data, rituximab-containing products can cause adverse developmental outcomes including B-cell lymphocytopenia in infants exposed to rituximab in-utero (see Clinical Considerations). There are no available data on RITUXAN HYCELA use in pregnant women to inform a drug-associated risk of major birth defects and miscarriage. In animal reproduction studies, intravenous administration of a rituximab product to pregnant cynomolgus monkeys during the period of organogenesis caused lymphoid B cell depletion in the newborn offspring at doses resulting in 80% of the exposure (based on AUC) of those achieved following a dose of 2 grams in humans. Reduced fetal weight and increased fetal lethality were observed following subcutaneous administration of hyaluronidase human in mice at a dose > 2700 times higher than the human dose. Comparable systemic exposure levels could occur in a pregnant patient following accidental intravenous administration of an entire vial of RITUXAN HYCELA (see Data). Advise pregnant women of the risk to a fetus.

Adverse outcomes in pregnancy occur regardless of the health of the mother or the use of medications. The background risk of major birth defects and miscarriage for the indicated population is unknown. The estimated background risk in the U.S. general population of major birth defects is 2%–4% and of miscarriage is 15%–20% of clinically recognized pregnancies.

Clinical Considerations

Fetal/Neonatal Adverse Reactions

Observe newborns and infants for signs of infection and manage accordingly.

Data

Human Data

Postmarketing data indicate that B-cell lymphocytopenia generally lasting less than six months can occur in infants exposed to rituximab in-utero. Rituximab was detected postnatally in the serum of infants exposed in-utero.

Animal Data

RITUXAN HYCELA for subcutaneous injection contains rituximab and hyaluronidase human [see Description (11)].

Rituximab Product:

- An embryo-fetal developmental toxicity study was performed on pregnant cynomolgus monkeys. Pregnant animals received rituximab via the intravenous route during early gestation (organogenesis period; post coitum days 20 through 50). Rituximab was administered as loading doses on post coitum (PC) Days 20, 21 and 22, at 15, 37.5 or 75 mg/kg/day, and then weekly on PC Days 29, 36, 43 and 50, at 20, 50 or 100 mg/kg/week. The 100 mg/kg/week dose resulted in 80% of the exposure (based on AUC) of those achieved following a dose of 2 grams in humans. Rituximab crosses the monkey placenta. Exposed offspring did not exhibit any teratogenic effects but did have decreased lymphoid tissue B cells.
- A subsequent pre-and postnatal reproductive toxicity study in cynomolgus monkeys was completed to assess developmental effects including the recovery of B cells and immune function in infants exposed to rituximab in utero. Animals were treated with a loading dose of 0, 15, or 75 mg/kg every day for 3 days, followed by weekly dosing with 0, 20, or 100 mg/kg dose. Subsets of pregnant females were treated from PC Day 20 through
postpartum Day 78, PC Day 76 through PC Day 134, and from PC Day 132 through delivery and postpartum Day 28. Regardless of the timing of treatment, decreased B cells and immunosuppression were noted in the offspring of rituximab-treated pregnant animals. The B-cell counts returned to normal levels, and immunologic function was restored within 6 months postpartum.

Hyaluronidase Human:
- In an embryo-fetal study, mice have been dosed daily by subcutaneous injection during the period of organogenesis with hyaluronidase human at dose levels up to 2,200,000 U/kg, which is > 2700 times higher than the human dose. The study found no evidence of teratogenicity. Reduced fetal weight and increased numbers of fetal resorptions were observed, with no effects found at a daily dose of 360,000 U/kg, which is > 450 times higher than the human dose.
- In a peri-and post-natal reproduction study, mice have been dosed daily by subcutaneous injection, with hyaluronidase human from implantation through lactation and weaning at dose levels up to 1,100,000 U/kg, which is > 1,300 times higher than the human dose. The study found no adverse effects on sexual maturation, learning and memory or fertility of the offspring.

8.2 Lactation
There are no data on the presence of rituximab or hyaluronidase human in human milk, the effect on the breastfed infant, or the effect on milk production. However, rituximab is detected in the milk of lactating cynomolgus monkeys, and IgG is present in human milk. Since many drugs including antibodies are present in human milk, advise a lactating woman not to breastfeed during treatment and for at least 6 months after the last dose of RITUXAN HYCELA due to the potential for serious adverse reactions in breastfed infants.

8.3 Females and Males of Reproductive Potential
Rituximab-containing products can cause fetal harm [see Use in Specific Populations (8.1)].

Contraception
Females
Females of childbearing potential should use effective contraception while receiving RITUXAN HYCELA and for 12 months following treatment.

8.4 Pediatric Use
The safety and effectiveness of RITUXAN HYCELA in pediatric patients have not been established.

8.5 Geriatric Use
Of the total number of subjects in the SABRINA, MabEase, and SAWYER studies, 37% were 65 and over, while 10% were 75 and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

11 DESCRIPTION
RITUXAN HYCELA is a combination of rituximab and hyaluronidase human. Rituximab is a genetically engineered chimeric murine/human monoclonal IgG1 kappa antibody directed against the CD20 antigen. Rituximab has an approximate molecular weight of 145 kD. Rituximab has a binding affinity for the CD20 antigen of approximately 8.0 nM. Rituximab is produced by mammalian cell (Chinese Hamster Ovary) suspension culture in a nutrient medium containing the antibiotic gentamicin. Gentamicin is not detectable in the final product.
Recombinant human hyaluronidase is an endoglycosidase used to increase the dispersion and absorption of co-administered drugs when administered subcutaneously. It is produced by mammalian (Chinese Hamster Ovary) cells containing a DNA plasmid encoding for a soluble fragment of human hyaluronidase (PH20). It is a glycosylated single-chain protein with an approximate molecular weight of 61 kD.

RITUXAN HYCELA (rituximab and hyaluronidase human) Injection is a colorless to yellowish, clear to opalescent solution supplied in sterile, preservative-free, single-dose vials for subcutaneous administration.

RITUXAN HYCELA is supplied as 1,400 mg rituximab and 23,400 Units hyaluronidase human per 11.7 mL in single-dose vials or 1,600 mg rituximab and 26,800 Units hyaluronidase human per 13.4 mL in single-dose vials. Each mL of solution contains rituximab (120 mg), hyaluronidase human (2,000 Units), L-histidine (0.53 mg), L-histidine hydrochloride monohydrate (3.47 mg), L-methionine (1.49 mg), polysorbate 80 (0.6 mg), α,α-trehalose dihydrate (79.45 mg), and Water for Injection.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Rituximab is a monoclonal antibody that targets the CD20 antigen expressed on the surface of pre-B and mature B-lymphocytes. Upon binding to CD20, rituximab mediates B-cell lysis. Possible mechanisms of cell lysis include complement dependent cytotoxicity (CDC) and antibody dependent cell mediated cytotoxicity (ADCC). Hyaluronan is a polysaccharide found in the extracellular matrix of the subcutaneous tissue. It is depolymerized by the naturally occurring enzyme hyaluronidase. Unlike the stable structural components of the interstitial matrix, hyaluronan has a half-life of approximately 0.5 days. Hyaluronidase human increases permeability of the subcutaneous tissue by temporarily depolymerizing hyaluronan. In the doses administered, hyaluronidase human in RITUXAN HYCELA acts locally.

The effects of hyaluronidase human are reversible and permeability of the subcutaneous tissue is restored within 24 to 48 hours.

Hyaluronidase human has been shown to increase the absorption rate of a rituximab product into the systemic circulation when given in the subcutis of Göttingen Minipigs.

12.2 Pharmacodynamics

Peripheral B-cell counts declined to levels below normal following a dose of rituximab by intravenous infusion. In patients treated with rituximab for hematological malignancies, B cell recovery began within 6 months of treatment and generally returned to normal levels within 12 months after completion of therapy, although in some patients this may take longer.

Follicular Lymphoma (FL)
Peripheral B-cell counts decline to levels below normal following the first cycle of rituximab and are maintained during treatment with RITUXAN HYCELA. After stopping RITUXAN HYCELA treatment, B-cell repletion followed similar kinetics to that of rituximab with B-cell repletion beginning after 6 months of stopping treatment, although in some patients this may take longer.

Chronic Lymphocytic Leukemia (CLL)
Following the first cycle of treatment of rituximab, B-cells begin to deplete, with 28% of patients B-cell depleted at pre-dose Cycle 2 in the SAWYER study. An increase in the proportion of B-cell depleted patients was observed with subsequent cycles of RITUXAN HYCELA and by Cycle 6, 96% of patients were depleted. Patients remained B-cell depleted until the month 9 follow-up visit, where signs of repletion were seen.
12.3 Pharmacokinetics

The geometric mean rituximab exposures are provided in Table 4. The pharmacokinetic properties of rituximab following the administration of RITUXAN HYCELA in the approved indications are provided in Table 5. The elimination of rituximab was characterized by a time-dependent process that occurred early in therapy and a time-independent process.

Table 4: Rituximab Exposure Values following Subcutaneous Administration of RITUXAN HYCELA

<table>
<thead>
<tr>
<th>Study</th>
<th>Cycle</th>
<th>Rituximab</th>
</tr>
</thead>
<tbody>
<tr>
<td>FLc</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cmax, mcg/mL (CV%)</td>
<td>SABRINA</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td></td>
<td>18</td>
</tr>
<tr>
<td>Ctrough, mcg/mL (CV%)</td>
<td></td>
<td>7</td>
</tr>
<tr>
<td></td>
<td></td>
<td>18</td>
</tr>
<tr>
<td>AUC_TAU, mcg•day/mL (CV%)</td>
<td></td>
<td>7</td>
</tr>
<tr>
<td></td>
<td></td>
<td>18</td>
</tr>
<tr>
<td>CLLd</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cmax, mcg/mL (CV%)</td>
<td>SAWYER</td>
<td>6</td>
</tr>
<tr>
<td>Ctrough, mcg/mL (CV%)</td>
<td></td>
<td>5</td>
</tr>
<tr>
<td>AUC_TAU, mcg•day/mL (CV%)</td>
<td></td>
<td>5</td>
</tr>
</tbody>
</table>

* Pharmacokinetic parameters are presented as geometric mean unless otherwise specified.
* For study design information, see Clinical Studies (14).
* RITUXAN HYCELA 1,400 mg/23,400 Units (1,400 mg rituximab and 23,400 Units hyaluronidase human)
* RITUXAN HYCELA 1,600 mg/26,800 Units (1,600 mg rituximab and 26,800 Units hyaluronidase human)
* Based on predicted values

In the SABRINA study, the geometric mean Ctrough in the RITUXAN HYCELA arm was higher than in the rituximab arm with a geometric mean ratio (Ctrough, RITUXAN HYCELA/Ctrough, rituximab) of 1.52 (90% CI: 1.36, 1.70) at Cycle 7 [see Clinical Studies (14.1)]. In the SAWYER study, the geometric mean Ctrough in the RITUXAN HYCELA arm was higher than in the rituximab arm with an adjusted geometric mean ratio of 1.53 (90% CI: 1.27–1.85) at Cycle 5 [see Clinical Studies (14.3)].
Table 5: Pharmacokinetic Parameters of Rituximab following Subcutaneous Administration of RITUXAN HYCELA

<table>
<thead>
<tr>
<th></th>
<th>FL</th>
<th>CLL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absorption</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absolute Bioavailability(^{b})</td>
<td>0.646 ((0.634–0.659)^{d})</td>
<td>0.634 ((0.602–0.665)^{d})</td>
</tr>
<tr>
<td>Distribution</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Volume of Central compartment (L)</td>
<td>4.06 (26)</td>
<td>4.80 (18)</td>
</tr>
<tr>
<td>Apparent Volume of Distribution at steady state(^{c}) (L)</td>
<td>8.09 (19)</td>
<td>8.52 (13)</td>
</tr>
<tr>
<td>Elimination</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Terminal Half-life (days)</td>
<td>34.1 (27)</td>
<td>32 (24)</td>
</tr>
<tr>
<td>Clearance (L/day)</td>
<td>0.18 (34)</td>
<td>0.204 (31)</td>
</tr>
</tbody>
</table>

\(^{a}\) Parameters represented as geometric mean (%CV) unless otherwise specified

\(^{b}\) Compared to a rituximab product administered intravenously

\(^{c}\) Volume of central compartment and peripheral compartment

\(^{d}\) 95% CI

Specific Populations

The pharmacokinetics of rituximab and hyaluronidase human in children and adolescents is unknown. The effect of either renal or hepatic impairment on the pharmacokinetics of rituximab and hyaluronidase human is unknown.

Drug Interaction Studies

The drug interaction potential of rituximab and hyaluronidase human is unknown.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No long term animal studies have been performed to establish the carcinogenic or mutagenic potential of RITUXAN HYCELA or rituximab, or to determine potential effects on fertility in males or females.

RITUXAN HYCELA contains hyaluronidase human. Hyaluronidase is found in most tissues of the body. Long-term animal studies have not been performed to assess the carcinogenic or mutagenic potential of hyaluronidase human. In addition, when hyaluronidase human was administered to cynomolgus monkeys for 39 weeks at dose levels up to 220,000 U/kg, which is > 90 times higher than the human dose, no evidence of toxicity to the male or female reproductive system was found through periodic monitoring of in-life parameters, e.g., semen analyses, hormone levels, menstrual cycles, and also from gross pathology, histopathology and organ weight data.

14 CLINICAL STUDIES

14.1 Follicular Lymphoma

The SABRINA study [NCT01200758] was a randomized, two-stage, open-label, multicenter study that enrolled a total of 410 patients with previously untreated, CD20-positive follicular lymphoma of Grade 1, 2 or 3a requiring therapy. The study design is identical in stage 1 and 2. Patients were randomized (1:1) to receive either a rituximab product by intravenous infusion 375 mg/m\(^2\) for 8 cycles or 1 cycle of a rituximab product by intravenous infusion 375 mg/m\(^2\) followed by 7 cycles of RITUXAN HYCELA 1,400mg/23,400 Units (1,400 mg rituximab and 23,400 Units hyaluronidase human) both every 3 weeks in combination with a total of 6–8 cycles of CHOP or 8 cycles of CVP chemotherapy. Patients underwent interim staging after 4 cycles. Patients who received R-CHOP and achieved a CR, CRu, PR or SD at the interim assessment could receive either 4 more cycles of R-CHOP or 2 cycles of R-CHOP followed by 2 cycles of
monotherapy with rituximab product or RITUXAN HYCELA depending on randomization arm (i.e., a total of 8 cycles of rituximab product or RITUXAN HYCELA). Patients with at least a PR after combination treatment with chemotherapy continued with single agent maintenance treatment administered every 8 weeks for 24 months with rituximab product or RITUXAN HYCELA as per their randomization (i.e., total of 12 cycles of maintenance treatment).

Randomization was stratified by: underlying chemotherapy backbone (CHOP vs CVP), Follicular Lymphoma International Prognostic Index (FLIPI) (low-risk vs. intermediate-risk vs. high-risk), and region (Europe and North America vs. South and Central America vs Asia). The main outcome measure for Stage 1 was the estimated ratio of observed rituximab serum $C_{\text{trough SC}}/C_{\text{trough IV}}$ at Cycle 7 of combination treatment with chemotherapy every 3 weeks. The main outcome measure for Stage 2 was the investigator-assessed ORR consisting of CR, CRu, and PR at the completion of combination treatment with chemotherapy. Additional outcome measures were CRR (CR and CRu) at the end of completion of combination treatment with chemotherapy, ORR and CRR at the end of completion of maintenance treatment, and time-to-event endpoints (progression-free survival (PFS), and overall survival (OS)).

Of all randomized patients, the median age was 57 years, median BSA was 1.83 m², 53% were females, and 86% were Caucasian, 45% had high risk or 34% had intermediate risk FLIPI score, and 54% had Ann Arbor Stage IV disease at study entry. Ninety percent of patients completed all 8 cycles of combination treatment with chemotherapy, and 70% of patients completed 20 cycles of both combination and maintenance treatment. Median treatment duration was 27.1 months in both groups. The median number of cycles received was 20 in both groups.

The PK results for the primary endpoint in Stage 1, rituximab $C_{\text{trough}}$ at Cycle 7 (i.e., 21 days after Cycle 7 rituximab administration), demonstrated that RITUXAN HYCELA 1,400 mg/23,400 Units was non-inferior compared with rituximab at 375 mg/m² in patients receiving combination treatment with chemotherapy [see Clinical Pharmacology (12.3)]. The efficacy results for RITUXAN HYCELA were comparable with rituximab and are presented in Table 6.
### Table 6: Efficacy Results for SABRINA Study

<table>
<thead>
<tr>
<th>Parameter</th>
<th>RITUXAN HYCELA n=205</th>
<th>Rituximab n=205</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Overall Response Rate at End of combination treatment with chemotherapy</strong>&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of responders (CR/CRu, PR)</td>
<td>173</td>
<td>174</td>
</tr>
<tr>
<td>Overall response (CR/CRu, PR) rate (% [95% CI])</td>
<td>84% [79;89]</td>
<td>85% [79;90]</td>
</tr>
<tr>
<td>Difference in overall response rates&lt;sup&gt;b&lt;/sup&gt; [95% CI]</td>
<td>-0.5% [-7.7;6.8]</td>
<td></td>
</tr>
<tr>
<td>Number of complete responders (CR/CRu)</td>
<td>66</td>
<td>66</td>
</tr>
<tr>
<td>Complete response (CR/CRu) rate (% [95% CI])</td>
<td>32% [26;39]</td>
<td>32% [26;39]</td>
</tr>
<tr>
<td>Difference in complete response rates&lt;sup&gt;b&lt;/sup&gt; [95% CI]</td>
<td>0.0% [-9.3;9.3]</td>
<td></td>
</tr>
<tr>
<td><strong>Overall Response Rate at End of Maintenance</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of patients treated in maintenance (n)</td>
<td>172</td>
<td>178</td>
</tr>
<tr>
<td>Number of responders (CR/CRu, PR)</td>
<td>134</td>
<td>139</td>
</tr>
<tr>
<td>Overall response (CR/CRu, PR) rate (% [95% CI])</td>
<td>78% [71;84]</td>
<td>78% [71;84]</td>
</tr>
<tr>
<td>Difference in overall response rates&lt;sup&gt;b&lt;/sup&gt; [95% CI]</td>
<td>-0.2 [-9.2;8.8]</td>
<td></td>
</tr>
<tr>
<td>Number of complete responders (CR/CRu)</td>
<td>87</td>
<td>100</td>
</tr>
<tr>
<td>Complete response (CR/CRu) rate (% [95% CI])</td>
<td>51% [43;58]</td>
<td>56% [49;64]</td>
</tr>
<tr>
<td>Difference in complete response rates&lt;sup&gt;b&lt;/sup&gt; [95% CI]</td>
<td>-5.6 [-16.4;5.2]</td>
<td></td>
</tr>
<tr>
<td><strong>Progression-free survival</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of patients with event</td>
<td>50 (24%)</td>
<td>57 (28%)</td>
</tr>
<tr>
<td>Hazard Ratio [95% CI] (unstratified Cox model)</td>
<td>0.84 [0.57;1.23]</td>
<td></td>
</tr>
<tr>
<td><strong>Overall survival</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of patients with event</td>
<td>16 (7.8%)</td>
<td>20 (9.8%)</td>
</tr>
<tr>
<td>Hazard Ratio [95% CI] (unstratified Cox model)</td>
<td>0.81 [0.42;1.57]</td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup> Stage 2 main outcome measure was ORR at the end of combination treatment with chemotherapy; however pooled results which were preplanned are presented in this Table.

Response rates based on investigator assessment.

Response rates at end of maintenance based on patients who received at least one cycle of maintenance treatment (n).

<sup>b</sup> Difference in response rates (RITUXAN HYCELA minus rituximab).

### 14.2 Diffuse Large B-Cell Lymphoma (DLBCL)

The MabEase study [NCT01649856] enrolled a total of 576 patients with previously untreated CD20-positive DLBCL. Patients were randomized (2:1) to receive either a rituximab product by intravenous infusion, 375 mg/m<sup>2</sup> for 8 cycles or 1 cycle of an rituximab product by intravenous infusion 375 mg/m<sup>2</sup> followed by 7 cycles of RITUXAN HYCELA 1,400 mg/23,400 Units (1,400 mg rituximab and 23,400 Units hyaluronidase human), both in combination with up to 6–8 cycles of CHOP chemotherapy, every 14 (CHOP-14) or 21 days (CHOP-21). Randomization was stratified by: age (<60 years, ≥60 years), International Prognostic Index (IPI) risk category (low, low-intermediate, high-intermediate, high), and chemotherapy regimen (CHOP-21 or CHOP-14). The main outcome measure was investigator-assessed complete response rate (CR/CRu) at the end of combination treatment with chemotherapy. Additional outcome measures were time-to-event endpoints (PFS and OS).

Of all randomized patients, 54% of patients were male, the median age was 64 years, 79% Caucasians, median BSA was 1.83 m<sup>2</sup>, 31% low risk or 30% low intermediate risk IPI score, 24% high intermediate risk, or 15% high risk IPI score and 42% of patients had Ann Arbor Stage IV disease. A total of 470 patients (82%) received 8 cycles of treatment. Median duration of
exposure to treatment was 4.9 months in both treatment groups. The median number of administrations/cycles (RITUXAN HYCELA or rituximab) was 8 in both groups. The efficacy results for RITUXAN HYCELA were comparable with rituximab and are presented in Table 7. The median observation time was approximately 28 months.

Table 7: Efficacy Results for MabEase Study

<table>
<thead>
<tr>
<th></th>
<th>RITUXAN HYCELA (n=381)</th>
<th>Rituximab (n=195)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Complete Response Rate (CR/CRu)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of responders (CR/CRu achieved)</td>
<td>179</td>
<td>82</td>
</tr>
<tr>
<td>Response rate (%,[95% CI])</td>
<td>47% [42;52]</td>
<td>42% [35;49]</td>
</tr>
<tr>
<td>Difference in response rates [95% CI]</td>
<td></td>
<td>4.9% [-3.6;13.5]</td>
</tr>
<tr>
<td><strong>Progression-free survival</strong>c</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of patients with event</td>
<td>104 (27%)</td>
<td>44 (23%)</td>
</tr>
<tr>
<td>Hazard Ratio [95% CI] (unstratified Cox model)</td>
<td>1.22 [0.85;1.73]</td>
<td></td>
</tr>
<tr>
<td><strong>Overall survival</strong>d</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of patients with event</td>
<td>63 (17%)</td>
<td>29 (15%)</td>
</tr>
<tr>
<td>Hazard Ratio [95% CI] (unstratified Cox model)</td>
<td>1.08 [0.70;1.68]</td>
<td></td>
</tr>
</tbody>
</table>

* Four patients in the RITUXAN HYCELA group and 1 patient in the rituximab group had their response downgraded due to their bone marrow data.

b Difference in response rates (RITUXAN HYCELA minus rituximab).

c Progression-free survival is defined as the time from randomization to the first occurrence of disease progression or relapse, or death from any cause.

d Overall survival is defined as the time from randomization until death from any cause.

14.3 Chronic Lymphocytic Leukemia (CLL)

The SAWYER study [NCT01292603] was a randomized, two-part, open-label, multicenter study that enrolled a total of 176 patients with previously untreated CLL. Patients were randomized (1:1) to receive either a rituximab product by intravenous infusion, 375 mg/m², in Cycle 1 followed by up to 5 cycles of rituximab, 500 mg/m², or rituximab, 375 mg/m², in Cycle 1 followed by subsequent cycles (2–6) of RITUXAN HYCELA 1,600 mg /26,800 Units (1,600 mg rituximab and 26,800 Units hyaluronidase human), both in combination with fludarabine and cyclophosphamide (FC) chemotherapy. The main outcome measure was the non-inferiority of the pharmacokinetic profile of RITUXAN HYCELA compared to rituximab.

The patient population comprised 96% Caucasians, 65% males, a median age of 60 years (range 25–78 years), median BSA of 1.9 m², 62% had Binet Stage B disease and 93% had typical CLL characterization.

The PK results demonstrated that RITUXAN HYCELA 1,600mg/26,800 Units serum rituximab Cₜᵋᵣᵤ level was non-inferior compared with rituximab at 500 mg/m² in patients receiving combination treatment with chemotherapy [see Clinical Pharmacology (12.3)].

An additional outcome measure in Part 2 was investigator-assessed response rates. Overall response rate was 85% (95% CI: 76; 92) in RITUXAN HYCELA and 81% (95% CI: 71; 88) in the rituximab groups. Overall the response rates were comparable between RITUXAN HYCELA and rituximab with a difference in response rate of 4.6% (95% CI:-7.2; 16.3). Complete response
rate point estimates were 26% (95% CI: 17; 37) and 33% (95% CI: 23; 44) in the RITUXAN HYCELA and rituximab groups, respectively.

14.4 Patient Experience
Previously untreated adult patients outside of the United States with CD20+ diffuse large B-cell lymphoma (DLBCL) or CD20+ follicular non-Hodgkin’s lymphoma (FL) Grades 1, 2, or 3a were randomized to receive a standard chemotherapy regimen (CHOP, CVP, or bendamustine) and either RITUXAN HYCELA 1,400mg/23,400 Units at Cycles 2–4 (after the first cycle with intravenous rituximab) or a rituximab product by intravenous infusion at Cycles 1–4. After the fourth cycle, patients were crossed over to the alternative route of administration for the remaining 4 cycles. After Cycle 8, 477 of 620 patients (77%) reported preferring subcutaneous administration of RITUXAN HYCELA over intravenous rituximab and the most common reason was that administration required less time in the clinic. After Cycle 8, 66 of 620 patients (11%) preferred rituximab intravenous administration and the most common reason was that it felt more comfortable during administration. Forty eight of 620 patients (7.7%) had no preference for the route of administration. Twenty nine subjects of 620 (4.7%) received Cycle 8 but did not complete the preference questionnaire.

16 HOW SUPPLIED/STORAGE AND HANDLING
RITUXAN HYCELA (rituximab and hyaluronidase human) Injection formulated for subcutaneous injection is supplied as a sterile preservative-free liquid solution in a single-dose vial. The following configurations are available:

Individually packaged single-dose vials:
- RITUXAN HYCELA 1,400 mg/23,400 Units (NDC 50242-108-01) providing 1,400 mg rituximab and 23,400 Units hyaluronidase human per 11.7 mL
- RITUXAN HYCELA 1,600 mg/26,800 Units (NDC 50242-109-01) providing 1,600 mg rituximab and 26,800 Units hyaluronidase human per 13.4 mL

Storage and Stability
Store RITUXAN HYCELA vials in the refrigerator at 2ºC–8ºC (36ºF–46ºF) in the original carton to protect from light. Do not freeze.

17 PATIENT COUNSELING INFORMATION
Advise the patient to read the FDA-approved patient labeling (Medication Guide).

Severe Mucocutaneous Reactions
Advise patients to contact their healthcare provider immediately for symptoms of severe mucocutaneous reactions, including painful sores or ulcers on the lips or mouth, blisters, peeling skin, rash, and pustules [see Warnings and Precautions (5.1)].

Hepatitis B Virus Reactivation
Advise patients to contact their healthcare provider immediately for symptoms of hepatitis including worsening fatigue or yellow discoloration of skin or eyes [see Warnings and Precautions (5.2)].

Progressive Multifocal Leukoencephalopathy (PML)
Advise patients to contact their healthcare provider immediately for signs and symptoms of PML, including new or changes in neurological symptoms such as confusion, dizziness or loss of balance, difficulty talking or walking, decreased strength or weakness on one side of the body, or vision problems [see Warnings and Precautions (5.3)].

Hypersensitivity and Other Administration Reactions
Inform patients about the signs and symptoms of hypersensitivity and administration-related reactions. Advise patients to contact their healthcare provider immediately to report symptoms of
administration-related reactions including dizziness, nausea, chills, fever, vomiting, diarrhea, urticaria, angioedema, breathing problems, or chest pain [see Warnings and Precautions (5.4)].

**Tumor Lysis Syndrome (TLS)**
Advise patients to contact their healthcare provider immediately for signs and symptoms of tumor lysis syndrome such as nausea, vomiting, diarrhea, and lethargy [see Warnings and Precautions (5.5)].

**Infections**
Advise patients to contact their healthcare provider immediately for signs and symptoms of infections including fever, cold symptoms (e.g., rhinorrhea or laryngitis), flu symptoms (e.g., cough, fatigue, body aches), earache or headache, dysuria, cold sores, and painful wounds with erythema [see Warnings and Precautions (5.6)].

**Cardiovascular Adverse Reactions**
Advise patients of the risk of cardiovascular adverse reactions, including ventricular fibrillation, myocardial infarction, and cardiogenic shock. Advise patients to contact their healthcare provider immediately to report chest pain and irregular heartbeats. [see Warnings and Precautions (5.7)]

**Renal Toxicity**
Advise patients of the risk of renal toxicity. Inform patients of the need for healthcare providers to monitor kidney function [see Warnings and Precautions (5.8)].

**Bowel Obstruction and Perforation**
Advise patients to contact their healthcare provider immediately for signs and symptoms of bowel obstruction and perforation, including severe abdominal pain or repeated vomiting [see Warnings and Precautions (5.9)].

**Embryo-Fetal Toxicity**
Advise a pregnant woman of the potential risk to a fetus. Advise female patients that rituximab containing products can cause fetal harm if taken during pregnancy and to use effective contraception during treatment with RITUXAN HYCELA and for at least 12 months after the last dose of RITUXAN HYCELA. Advise patients to inform their healthcare provider of a known or suspected pregnancy [see Warnings and Precautions (5.11) and Use in Specific Populations (8.1, 8.3)].
Lactation
Advise women not to breastfeed during treatment with RITUXAN HYCELA and for 6 months after the last dose [see Use in Specific Populations (8.2)].

RITUXAN HYCELA™ [rituximab and hyaluronidase human]

Manufactured by:
Genentech, Inc.
A Member of the Roche Group
1 DNA Way
South San Francisco, CA 94080-4990
US License No.: 1048

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Jointly marketed by: Biogen and Genentech USA, Inc.
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**What is the most important information I should know about RITUXAN HYCELA?**

**RITUXAN HYCELA** can cause serious side effects that can lead to death, including:

- **Severe skin and mouth reactions.** Tell your healthcare provider or get medical help right away if you get any of these symptoms at any time during your treatment with RITUXAN HYCELA:
  - painful sores or ulcers on your skin, lips or in your mouth
  - blisters
  - peeling skin
  - rash
  - pustules

- **Hepatitis B virus (HBV) reactivation.** Before you receive RITUXAN HYCELA, your doctor will do blood tests to check for HBV infection. If you have had hepatitis B or are a carrier of hepatitis B virus, receiving RITUXAN HYCELA could cause the virus to become an active infection again. Hepatitis B reactivation may cause serious liver problems including liver failure, and death. Your healthcare provider will monitor you for hepatitis B infection during and for several months after you stop receiving RITUXAN HYCELA.
  
  Tell your healthcare provider right away if you get worsening tiredness, or yellowing of your skin or white part of your eyes during treatment with RITUXAN HYCELA.

- **Progressive Multifocal Leukoencephalopathy (PML).** PML is a rare, serious brain infection caused by a virus that can happen in people who receive RITUXAN HYCELA. People with weakened immune systems can get PML. PML can result in death or severe disability. There is no known treatment, prevention, or cure for PML.
  
  Tell your healthcare provider right away if you have any new or worsening symptoms or if anyone close to you notices these symptoms:
  - confusion
  - dizziness or loss of balance
  - difficulty walking or talking
  - decreased strength or weakness on one side of your body
  - vision problems, such as blurred vision or loss of vision

- **Serious allergic reactions and other severe reactions.**

  **Serious allergic reactions, and reactions due to release of certain substances by your body that can lead to death, can happen with rituximab products, including RITUXAN HYCELA.**

  **Skin reactions at or near the injection site (local), including injection site reactions, can happen with RITUXAN HYCELA.** Symptoms at or near the injection site may include: pain, swelling, hardness, redness, bleeding, itching, and rash. These reactions sometimes happen more than 24 hours after an injection of RITUXAN HYCELA.
  
  Tell your healthcare provider or get medical help right away if you get any of these symptoms during or after an injection of RITUXAN HYCELA:
  - hives (red itchy welts) or rash
  - itching
  - swelling of your lips, tongue, throat or face
  - sudden cough
  - shortness of breath, difficulty breathing, or wheezing
  - weakness
  - dizziness or feel faint
  - palpitations (feel like your heart is racing or fluttering)
  - chest pain
  - fever
  - chills or shaking chills

See “**What are the possible side effects of RITUXAN HYCELA?**” for more information about side effects.
What is RITUXAN HYCELA?
RITUXAN HYCELA is a prescription medicine used to treat adults with:

- **Follicular Lymphoma (FL):** alone or with certain chemotherapy medicines.
- **Diffuse Large B-Cell Lymphoma (DLBCL):** with certain other chemotherapy medicines in people who have not had previous treatment for their DLBCL.
- **Chronic Lymphocytic Leukemia (CLL):** with the chemotherapy medicines fludarabine and cyclophosphamide.

You can only receive RITUXAN HYCELA after you receive at least 1 full dose of a rituximab product by IV infusion. Read the rituximab by IV infusion Medication Guide for more information about severe infusion reactions, which usually happen during the first dose with a rituximab product given by IV infusion.

RITUXAN HYCELA is not for use to treat medical conditions other than cancers.

It is not known if RITUXAN HYCELA is safe and effective in children.

Before you receive RITUXAN HYCELA, tell your healthcare provider about all of your medical conditions, including if you:

- have had a severe reaction to a rituximab product or RITUXAN HYCELA
- have a history of heart problems, irregular heart beat or chest pain
- have lung or kidney problems
- have an infection or weakened immune system
- have or have had any severe infections including:
  - Hepatitis B virus (HBV)
  - Hepatitis C virus (HCV)
  - Cytomegalovirus (CMV)
  - Herpes simplex virus (HSV)
  - Parvovirus B19
  - Varicella zoster virus (chickenpox or shingles)
  - West Nile Virus
- have had a recent vaccination or are scheduled to receive vaccinations. You should not receive certain vaccines before or during treatment with RITUXAN HYCELA.
- are pregnant or plan to become pregnant. Talk to your healthcare provider about the risks to your unborn baby if you receive RITUXAN HYCELA during pregnancy. Females who are able to become pregnant should use effective birth control (contraception) during treatment with RITUXAN HYCELA and for **12 months** after the last dose of RITUXAN HYCELA. Talk to your healthcare provider about effective birth control.
- are breastfeeding or plan to breastfeed. It is not known if RITUXAN HYCELA passes into your breast milk. Do not breastfeed during treatment and for **at least 6 months** after your last dose of RITUXAN HYCELA.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

How will I receive RITUXAN HYCELA?

- **RITUXAN HYCELA** is given as an injection under the skin, in the stomach-area (abdomen).
- **RITUXAN HYCELA** is injected over 5 or 7 minutes.
- Your healthcare provider will prescribe medicines before the injection of RITUXAN HYCELA to help reduce side effects such as fever and chills.
- Your healthcare provider should monitor you for side effects for at least 15 minutes after you receive an injection of RITUXAN HYCELA.
- If you have CLL, your healthcare provider should prescribe medicines to help prevent certain infections during treatment and for up to 12 months following treatment with RITUXAN HYCELA.

Before each injection of RITUXAN HYCELA treatment, your healthcare provider or nurse will ask you questions about your general health. Tell your healthcare provider or nurse about any new symptoms.
What are possible side effects of RITUXAN HYCELA?

RITUXAN HYCELA can cause serious side effects, including:

- **See “What is the most important information I should know about RITUXAN HYCELA?”**

- **Tumor Lysis Syndrome (TLS).** TLS is caused by the fast breakdown of cancer cells. TLS can cause you to have:
  - kidney failure and the need for dialysis treatment
  - abnormal heart rhythm

  TLS can happen within 12 to 24 hours after an injection of RITUXAN HYCELA. Your healthcare provider may do blood tests to check for TLS. Your healthcare provider may give you medicine to help prevent TLS.

  Tell your healthcare provider right away if you have any of the following signs or symptoms of TLS:
  - nausea
  - vomiting
  - diarrhea
  - lack of energy

- **Serious infections.** Serious infections can happen during and after treatment with RITUXAN HYCELA, and can lead to death. Rituximab products can increase your risk of getting infections and can lower the ability of your immune system to fight infections. Types of serious infections that can happen with RITUXAN HYCELA include bacterial, fungal, and viral infections. After receiving RITUXAN HYCELA, some people have developed low levels of certain antibodies in their blood for a long period of time (longer than 11 months). Some of these people with low antibody levels developed infections. Tell your healthcare provider right away if you have any symptoms of infection:
  - fever
  - cold symptoms, such as runny nose or sore throat that do not go away
  - flu symptoms, such as cough, tiredness, and body aches
  - earache or headache
  - pain during urination
  - white patches in the mouth or throat
  - cuts, scrapes or incisions that are red, warm, swollen or painful

- **Heart problems.** RITUXAN HYCELA may cause chest pain, irregular heartbeats, and heart attack. Your healthcare provider may monitor your heart during and after treatment with RITUXAN HYCELA if you have symptoms of heart problems or have a history of heart problems. Tell your healthcare provider right away if you have chest pain or irregular heartbeats during treatment with RITUXAN HYCELA.

- **Kidney problems** RITUXAN HYCELA can cause severe kidney problems that can lead to death. Your healthcare provider should do blood tests to check how well your kidneys are working.

- **Stomach and serious bowel problems that can sometimes lead to death.** Bowel problems, including blockage or tears in the bowel, can happen if you receive RITUXAN HYCELA with chemotherapy medicines. Tell your healthcare provider right away if you have severe stomach-area (abdomen) pain or repeated vomiting during treatment with RITUXAN HYCELA.

Your healthcare provider will stop treatment with RITUXAN HYCELA if you have severe, serious or life-threatening side effects.

**The most common side effects of RITUXAN HYCELA in people with Follicular Lymphoma (FL) include:** infections, low white blood cell count, nausea, constipation, cough, and tiredness.

**The most common side effects of RITUXAN HYCELA in people with Diffuse Large B-cell Lymphoma (DLBCL) include:** infections, low white blood cell count, loss of hair, nausea, and low red blood cell count.

**The most common side effects of RITUXAN HYCELA in people with Chronic Lymphocytic Leukemia (CLL) include:** infections, low white blood cell count, nausea, low platelet count, fever, vomiting, and injection site redness.

These are not all of the possible side effects with RITUXAN HYCELA. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

**General information about the safe and effective use of RITUXAN HYCELA.**

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. You can ask your pharmacist or healthcare provider for information about RITUXAN HYCELA that is written for health professionals.

**What are the ingredients in RITUXAN HYCELA?**

**Active ingredient:** rituximab and hyaluronidase human.

**Inactive ingredients:** L-histidine, L-histidine hydrochloride monohydrate, L-methionine, polysorbate 80, α,α-trehalose dihydrate, and Water for Injection.

Manufactured by: Genentech, Inc., A Member of the Roche Group, 1 DNA Way, South San Francisco, CA  94080-4990
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